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MECHANISM OF ANAEMIA IN INFANCY

HUGH JOSEPHS

From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland

We speak of haemolytic anaemia as if we know what it is. We define it as an anaemia due to increased blood destruction, but it is not by measuring the blood destruction that we recognize it. This we do by the presence of a Van den Bergh reaction of more than the usual intensity. We do not know, however, how much the haemolytic process must be increased before it is reflected in an increased Van den Bergh reaction. It is quite possible that we recognize increase in haemolysis only when it is excessive, but that we entirely miss cases in which the increase is moderate.

In the so-called "nutritional anaemia" of infancy it has long been considered probable that there is increased blood destruction because of the finding of haemosiderosis at autopsy, although it must be remembered that in these cases death has occurred usually in the course of an intercurrent infection which may have been the cause of the increase in the haemolytic process. In the second place, in these cases there is also usually found at autopsy evidence of considerable activity of the haemopoietic tissue which is reflected in an increased reticulocyte count during life. Now it is hard to understand why, in the face of increased haemopoietic activity, the red cells and haemoglobin should remain at a level or decrease, unless the activity of the blood-forming process is balanced or exceeded by the activity of the destructive processes, whatever these are. In this work I have undertaken to study this balance between the formation and destruction of the elements of the blood in cases of anaemia occurring under various conditions in infants.

As a rough measure of the amount of blood destruction, I have used the excretion of urobilin in the stools. The quantitative determination in the urine is quite useless for this purpose because the amount excreted in the urine rarely exceeds ten per cent of the total urobilin

excretion, and this proportion varies within such wide limits from day to day as to give no conception of the total amount excreted. The method used is that of Elman and McMaster (1), varying only in a few details. The stool specimens, kept in the refrigerator in the dark, if not analyzed within a day of their collection, were ground up under water and strained through a fine sieve. The emulsion thus obtained was measured; 10 cc. were transferred to a stoppered cylinder and to this was added 30 cc. of acid alcohol made up as directed by Elman and McMaster. The acid-alcohol suspension was shaken a few times and allowed to stand over night in a dark place. The next day 5 cc. of the mixture, shaken up again, were transferred to a 10 cc. cylinder, and one drop of tincture of iodine and a small amount of powdered zinc acetate were added. The mixture was shaken and a freshly prepared saturated alcoholic solution of zinc acetate was added up to the 10 cc. mark. After standing for a minute or two, the mixture was filtered and the fluorescent filtrate diluted until its fluorescence was the same as that of a 1 to 30,000,000 acriflavine solution. For the details of the solution used and the method of calculation the original article must be consulted. In order to determine the actual urobilin excretion, pure urobilin was prepared by the method given in the article of Elman and McMaster, dissolved in acid alcohol 10 mg. to 100 cc. and used to standardize the method. This preparation of urobilin, when kept in the refrigerator in the dark, was stable over at least four months.

Included in the term "urobilin" are all the substances occurring in the stools, capable, when treated as above, of giving a green fluorescence in alcoholic zinc acetate solution. It is of no great moment whether the term "urobilin" is the correct one to use. It is convenient and as here defined has a definite meaning. I shall, however, enclose it in quotation marks so that there need be no quibbling over names.

The percentage of reticulocytes has been used as a measure of the rate of blood formation. The estimation of the reticulocytes was made in the simplest possible manner. A dust and grease-free glass slide was prepared with a thin film of cresyl blue. A fresh wet blood preparation was made, by taking a small drop of blood on a clean coverslip and inverting onto the prepared slide. After standing for at least 20 minutes the reticulocytes were counted against the total red

cells in a sufficient number of fields so that from 500 to 1,000 red cell were included.

In order to compare rates of blood formation and blood destruction use has been made of certain arbitrary units. These are open to obvious criticisms and are of a tentative nature. As an index of blood formation the ratio of percentage of reticulocytes to the total erythrocytes has been employed and a unit of blood formation is defined as 0.7 per cent of reticulocytes. As a measure of blood destruction the ratio of "urobilin" excreted per day to the total circulating haemoglobin has been chosen. *A unit of blood destruction is defined as a daily excretion of 0.4 mg. "urobilin" per gram circulating hemoglobin.* Circulating haemoglobin is obtained from the formula:

$$\text{Wt. (kg.)} \times \text{Hgb. (gms. per 100 cc.)} \times 0.76$$

on the assumption that blood volume constitutes 76 cc. per kilo of body-weight.

The figure for the blood destruction unit is based on studies made on normal children. Under conditions of stationary haemoglobin it is fair to assume that the rate of blood formation equals that of blood destruction. Under such conditions it is found that the units of blood destruction and blood formation are equal when calculated as above.

The first case to be discussed can be used as an example of the way the results are recorded both in the tables and in the charts.

CASE REPORTS[1]

Case 1 (table 1). E. S. Colored. Male. Age: 2 years. The child was born at term, weighing 7 lbs. He was breast fed for one year, then given cow's milk up to the present time, without the addition of any other food. Orange juice and cod-liver oil were occasionally given. He was said not to have had any infections up to the present. On admission he was found to have syphilis, for which he was treated during the course in the hospital. Two days after admission he was transfused. Examination showed a moderate general glandular enlargement; a systolic murmur, but no cardiac enlargement; a moderately enlarged liver, but no enlargement of the spleen. He was given the regular diet at the

[1] Not all the cases on which this work is based have been included, owing to the necessity of economizing space. The ones used here, therefore, owe their inclusion to the fact that they are the best for purposes of illustration.

beginning, and this was continued throughout this stay. The observations recorded here began four days after admission. Iron[2] was begun after four weeks.

Discussion of case 1. The first six columns in the table are simple enough. The seventh column gives the number of grams of circulating haemoglobin. This is calculated from the formula: wt. × Hgb × 0.76. In the ninth column are figures for the average "urobilin" excretion in milligrams per day during the period of collection as noted in the eighth column. In the tenth the figures denote the milligrams of "urobilin" per gram of haemoglobin. As stated above, it was found convenient for the sake of comparison to use the idea of units of haemopoietic and haemolytic activity that would be equivalent to each other. The figures in

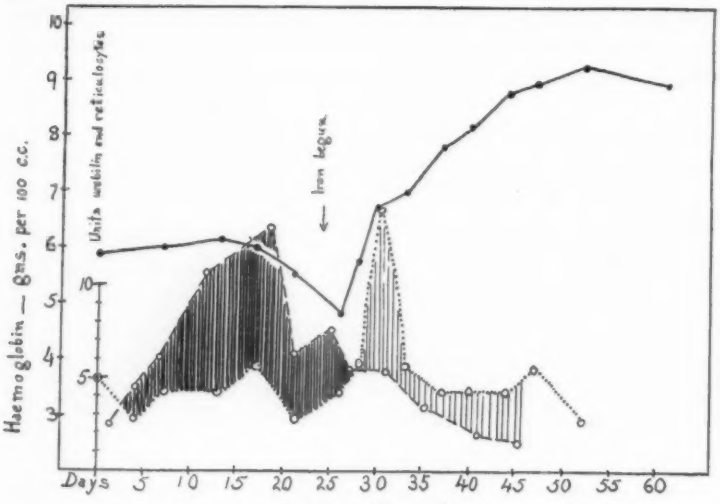

CHART I. (CASE 1)

the eleventh column are, therefore, obtained by dividing by 0.4 those in the tenth column, and the figures in the twelfth column by dividing those in the fifth column by 0.7.

In Chart I, as in all the others, the haemoglobin in grams per 100 cc. is represented by points joined by a solid line; the units of "urobilin" excretion by circles connected by a broken line; the units of reticulocytes percentage by circles connected by a dotted line. Where the "urobilin" units predominate, the area be-

[2] The dosage of iron was the same in all cases in which it was used: 10 per cent solution Ferric Ammonium Citrate 2 cc. per kilo of body-weight. The dosage of copper was likewise uniform: copper sulphate 0.5 per cent solution 1 cc. per kilo of body-weight.

TABLE 1

E. S. Case 1

DATE	WT.	HGB.	R.B.C.	RETICULOCYTES	C.I.	TOTAL HGB.	DATE	UROBILIN EXCRETION		UNITS		
								Mgs. per day	Mgs. per gm. hgb.	Urobilin	Reticulocytes	
	kg.	*gms. per 100 cc.*		*per cent*		*gms.*						
5/22/29	7.0	5.8		3.5		31	6/22–25	29	0.94	2.4	4.9	Regular ward diet
							25–27	58	1.8	4.5		
5/29	6.9	6.0		2		32	27–30	80	2.5	6.2	2.8	
6/ 4	7.3	6.2		3		34	1–4	150	4.4	11	4.2	
8	7.6	6.0		4		35	8–11	180	5.2	13	5.6	
12	7.6	5.5		2		32	11–13	80	2.5	6.2	2.8	Temp. normal
17	7.6	4 8		3		28	15–17	84	3.0	7.6	4.2	Fe begun 6/15/
19	7.6	5.7		4		33	17–19	73	2.2	5.5	5.7	
21	7.6	6.7		10		39	21–23	86	2.2	5.5	14	
24	7.6	7.0		4		41	23–25	57	1.4	3.5	5.7	
6/28	7.7	7.8		3		46					4.2	
7/ 1	8.0	8.2		—		50	30–7/4	40	0.8	2.0		
5	8.3	8.8		3		55	4–6	40	0.72	1.8	4.2	
8	8.3	8.9		4		56					5.7	
12	8.4	9.3		2		59					2.8	
7/22	9.2	8.8		<1		62					1	

TABLE 2

R. H. Case 2

5/ 7/30	7.8	5.3		<0.5		31					0.5	Temp. falling
9	7.8	6.7		1		40	5/8–10	12	0.4	1	1.4	Transfusion 5/8/30
15	7.7	7.3		2.5		43	17–19	15	0.35	0.9	3.5	Temp. rising. Em-
22	7.7	6.2		0		36	22–24	32	0.89	2.2	0	pyema
26	7.9	5.2		1		30	24–27	36	1.2	3.0	1.4	
5/29	7.5	5.3		<0.5		29	27–30	36	1.2	3.0	0.5	
6/ 9	7.1	4.7		<0.5		26	6/8–10	37	1.4	3.5	0.5	
6/16	7.3	4.5		<0.5		25					0.5	Transfusion 6/10/

TABLE 3

W. McK. Case 3

6/30/30	10.0	6.0		1		53	6/30–7/1	190	4.0	10	1.4	
7/ 2/30	10.0	7.1		3		54	7/1–3	410	7.4	18	4.2	
7/ 5	10.0	6.0		9		46					13	
7	10.0	6.1		4		46	3–9	160	3.5	8.7	5.7	
10	10.0	6.4		7		49	9–12	42	0.86	2.2	10	Temp. falling
14	10.0	6.7		8		51	12–14	56	1.2	3.0	11	Temp. normal
	10.0	—					14–17	52	1.0	2.5	—	
18	10.0	7.0		7		53					10	Cu + Fe begun
7/20	10.0	8.0		8		61	18–21	34	.56	1.4	11	7/18/

tween the line representing "urobilin" and that representing reticulocytes is heavily shaded; where reticulocyte units predominate the area between the two lines is lightly shaded. Red cells, in those cases in which counts were included, will be represented by crosses connected by a broken line.

In this case it is clearly seen that when the rate of blood destruction as represented by units of "urobilin" excretion exceeds the rate of formation as represented by reticulocyte units, the haemoglobin tends eventually to fall, even though the reticulocyte percentage is well above a point ordinarily considered normal. Just as soon as the rate of blood formation predominates over that of blood destruction the haemoglobin rises.

Case 2 (table 2). R. H. White. Male. Age: 20 months. The child was born at term, weighing 9 lbs. He was breast fed up to 11 months and had done well up to that time. He then developed an upper respiratory infection accompanied by diarrhea. From that time on he had frequent colds and became gradually anaemic. He finally developed pneumonia about a week before his admission to the hospital. On examination he was found to have, in addition to the pneumonia, a slight general glandular enlargement and an enlarged spleen. W. B. C. 16,000 with 88 per cent polymorphonuclears. He developed empyema and eventually died two months later. (For course during the period of study see table 2.)

Discussion of case 2. In the preceding case there was a retardation of recovery due to a continued mild infection. In this case there was no recovery except for a short period following the first transfusion. Later transfusion had no effect. The extremely low reticulocyte count points to a hypoplasia of the haemopoietic tissue, and this probably explains the fall in haemoglobin, for the rise in "urobilin" excretion is very moderate and, as will be seen later, even a considerable preponderance of blood destruction may not be accompanied by much reduction in haemoglobin as long as the haemopoietic tissue shows evidence of activity.

Case 3 (table 3). W. McK. White. Male. Age: 18 months. The family history has no bearing on the etiology of the anaemia. The child was born at term, weighing 9 lbs. He was breast fed for 1 month, then given condensed milk with orange juice and cod-liver oil up to 8 months. At this time his haemoglobin was 75 per cent (10.5 g. per 100 cc.). He had an attack of dysentery from which he recovered completely, and continued to do well for the next 10 months. He was then admitted to the hospital with a severe pneumonia of about two days' duration. Jaundice was present.

Discussion on case 3. Here, the infection caused a haemolytic type of anaemia. In this case the stage of recovery began before the temperature had returned to normal, but the rise in haemoglobin was slow, when one considers the preponderance of haemopoietic activity, until copper and iron were given. More examples of this relative failure of the haemoglobin to respond as one might expect will appear and will be discussed later.

Case 4 (table 4). H. C. Colored. Female. Age: 13 months. The child was born at term, weighing about 7 lbs. She was breast fed up to the time of admission, with the daily addition of vegetables, cereal and egg, but no cod-liver oil or orange juice. She was admitted with a pneumonia of two days' duration.

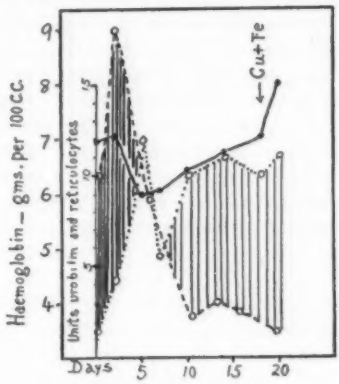

CHART II. (CASE 3)

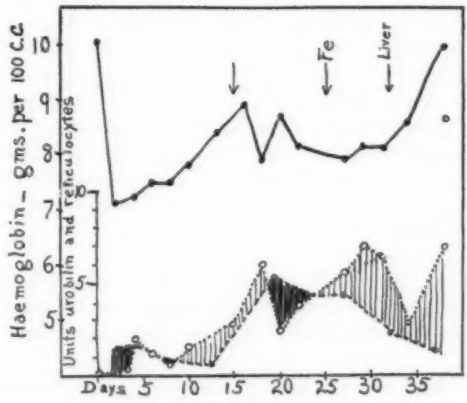

CHART III. (CASE 4)

There was a slight cervical glandular enlargement, and the liver and spleen were just palpable. The haemoglobin on admission, two days before the first haemoglobin value recorded in the table, was 70 per cent (10.1 g. per 100 cc.). W. B. C. 5,100 with about 60 per cent lymphocytes. On May 24 the white count had

risen to 8,800 and on May 26 it was 28,000 with 85 per cent polymorphonuclears. Coincidently with this rise in white cells the condition of the patient, which had been critical, improved markedly.

Discussion of case 4. This case is to be contrasted with the preceding one, for here we are dealing with a haemopoietic reaction that only just missed being aplastic. The fall in haemoglobin is more than would theoretically be expected if the normal average life of the red cell is about thirty days, for the "urobilin" excretion was not increased to any appreciable extent, but it is quite possible that the fall in haemoglobin is more apparent than real. Concentration of the blood due to dehydration in the critically ill child, as well as the difference in the haemoglobinometer used in the first determination (Sahli), might account for some of the fall. During the period of recovery the type of reaction changed, for here we see a temporary haemolytic reaction, with even a slight preponderance of blood destruction, that was capable of halting the recovery which had been well on its way.

Case 5 (table 5). R. J. Colored. Male. Age: 12 months. The child was born at term. His feeding was partly breast milk and partly cow's milk with occasional addition of other food. He was admitted to the hospital with pneumonia of about four days' duration. The temperature reached normal four days after admission and this study was started the next day.

Discussion of case 5. The preponderance of blood destruction in this case at the beginning of observation was considerable, yet the haemoglobin remained more or less constant, until iron was administered. After a short phase of rising haemoglobin following closely the curve given in a preceding article (2) as the average course of haemoglobin when iron alone was administered, copper was given and as in the preceding case the haemoglobin rose sharply, although there was no preponderance of blood formation. In other words, the haemoglobin appears to vary to some extent independently of the balance between formation and destruction. A possible explanation for this behavior of the haemoglobin will be presented later.

Case 6 (table 6). J. H. White. Male. Age: 1 year. The child was admitted for a haemangioma of the orbit and nothing is known of the previous feeding history. His eye was enucleated just before the observations recorded here were begun.

Discussion of case 6. In this case the reaction of red cells and haemoglobin is about what would be expected. No iron was given because there was an adequate rise in reticulocytes without it following the operation and we wished to see what copper alone would do under the circumstances. It is interesting to note that the haemoglobin did not rise as sharply as the red cells until the copper was given. This as a single occurrence is, of course, without special significance, but we shall see the same phenomenon among the cases that follow.

TABLE 4

H. C. Case 4

DATE	WT.	HGB.	R.B.C.	RETICULOCYTES	C.I.	TOTAL HGB.	DATE	UROBILIN EXCRETION		UNITS		
								Mgs. per day	Mgs. per gm. hgb.	Urobilin	Reticulocytes	
	kg.	*gms. per 100 cc.*		*per cent*		*gms.*						
5/23/29	7.1	7.2		0		39	23–24	18	0.47	1.2	0	
24	7.1	0.3		<0.5		39					0.5	
25	6.8	0.3		1.5		38	24–27	25	0.65	1.6	2.1	
27	6.9	0.5		1		39					1.4	
29	6.8	0.5		0.5		39					<1	Temp. falling
5/31	6.7	7.8		1		40					1.4	Regular diet
6/ 3	6.5	8.4		1		41	6/1–4	10	0.25	0.6	1.4	
5	6.4	8.9		2		43					2.8	
8	6.5	7.8		4.5		38					6.5	
10	6.5	8.7		2		43	8–11	90	2.1	5.2	2.8	
12	6.7	8.2		2.5		42					3.5	
							11–15	70	1.7	4.2		Fe begun 6/15/
17	7.1	7.9		4		43	15–19	75	1.8	4.5	5.7	
19	7.2	8.2		5		45					7.1	
21	7.3	8.2		4.5		46	21–23	41	0.89	2.2	6.5	
24	7.3	8.6		3		48					2.8	Liver 6/22
6/28	7.4	10.0		5		56	26–28	31	0.55	1.4	7.1	

TABLE 5

R. J. Case 5

11/ 8/30		5.2		1		40	9–11	235	5.9	15	1.4	Regular diet
12	10.2	5.3		1.5		41	11–13	150	3.7	9	2	Normal temp.
19	10.2	5.6		4		43	22–24	110	2.5	6	5.7	
25	10.2	5.7		2		44	24–26	80	1.8	4.5	2.8	Fe begun 11/25/
11/29	10.2	6.7		5		52	26–28	92	2.0	5.0	—	
12/ 1	10.2	6.7		6		52	29–12/1	100	1.9	4.8	7.1	
5	10.2	7.4		3		57	1–3	63	1.2	3.0	8.6	
10	10.2	7.6		—		59					4.2	
13	10.2	7.7		2		60	10–13	56	0.96	2.4		
14	10.2	7.7		1		60					2.8	Cu begun 12/13/
16	10.2	8.5		1		66					1.4	
12/18	10.2	9.5		1		74					1.4	
											1.4	

TABLE 6

J. H. Case 6

1/17/30	10.0	5.7	2.3	4	0.9	43					5.7	Regular diet
20	10.0	7.0	2.6	8.5	0.95	53	18–21	58	1.1	2.8	12	
24	10.0	7.4	3.9	10.0	0.7	56	21–24	70	1.2	3.1	14	Cu begun 1/24
26	10.0	8.9	4.2	6.0	0.75	68	24–27	72	1.05	2.6	8.6	
28	10.0	9.7	4.3	5	0.8	74	27–30	75	1.0	2.5	7	
30	10.0	9.4	3.9	6	0.85	72					8.6	

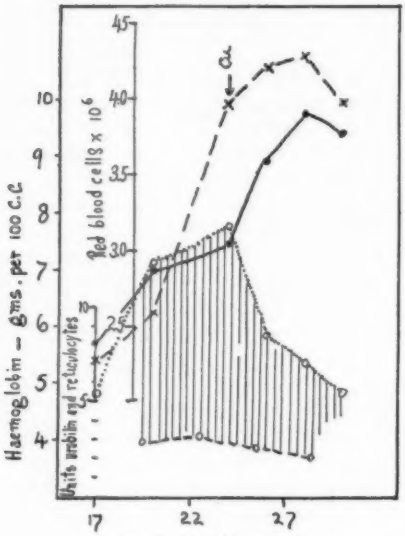

CHART IV. (CASE 6)

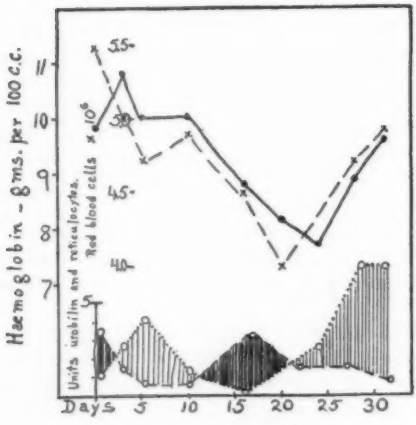

CHART V. (CASE 7)

Case 7 (table 7). J. S. Colored. Male. Age: 7 months. The child, up to the time he developed pneumonia a few days before admission to the hospital, had been quite well, receiving a well-balanced diet, and developing normally. This study was begun when the pneumonia for which he was admitted was subsiding. Two weeks later there was a rise of temperature and a return of the signs of pneumonia, which lasted for about 10 days and then cleared entirely.

Discussion of case 7. Here again the course of the red cells and haemoglobin is about what one should expect. The profound effect of the hypoplastic reaction during the period of exacerbation of the pneumonia on the course of haemoglobin and red cells is striking.

Case 8 (table 8). F. W. Colored. Male. Age: 6 months. The child had always been quite well up to the beginning of the pneumonia for which he was admitted to the hospital. The crisis occurred 5 days after the study was begun.

Case 9 (table 9). J. S. White. Male. Age: 9 months. The child had done only fairly well though on an adequate diet. He was under weight as the result of an attack of diarrhea he had had at about 5 months of age. He was subject to upper respiratory infections and was admitted to the hospital with pneumonia that developed from one of these. He was found on examination to have chronically infected tonsils and slight cervical glandular enlargement.

Discussion of cases 8 and 9. These two are good cases for comparison, for they illustrate the fact that the haemoglobin may vary independently of the red cells and of the preponderance of blood formation. In case 8 where the preponderance of haemopoietic activity was very slight, the red cells showed little tendency to rise over a period of eight days while the haemoglobin rose satisfactorily. In case 9 where the preponderance of blood formation was great, the red cells rose very rapidly while the haemoglobin remained more or less stationary.

Case 10 (table 10). H. H. White. Male. Age: 14 months. The child was born at term, weighing 7 lbs. He was breast fed two weeks, then given cow's milk mixtures with the addition of cod-liver oil and orange juice up to the time of admission. No other food had been given. Up to two weeks before admission he was quite well, then developed an otitis media and a little later pneumonia.

Discussion of case 10. In this case there was at first the preponderance of haemolytic activity with a very low reticulocyte count characteristic of the severe infection. Accompanying this phase was a fall in both red cells and haemoglobin. As soon as the infection was over there occurred a preponderance of blood formation with a rise in both red cells and haemoglobin; then a quiescent stage during which formation and destruction were about at the same point. As soon as iron was given the reticulocytes rose, and at the same time the red cells increased rapidly. The haemoglobin, on the other hand, did not rise to any significant extent until copper was given, eight days later.

Case 11 (table 11). P. M. White. Male. Age: 15 months. The child was born prematurely weighing less than four pounds. His feeding was fairly well taken care of and he received vegetables and eggs from ten months on. This food was well taken. He had frequent respiratory infections including one rather

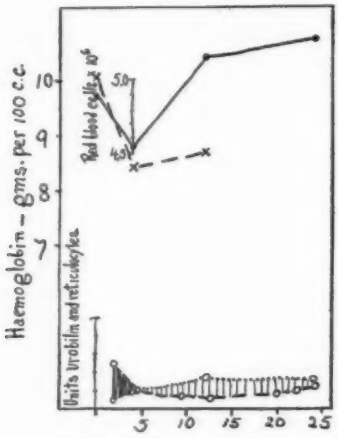

CHART VI. (CASE 8)

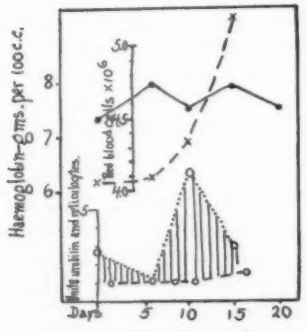

CHART VII. (CASE 9)

severe one with otitis media, and what was thought to be pneumonia at five months of age. At one year of age he was said to be very pale; at that time one of his ears was discharging and he was not gaining well. He was admitted at 15 months of age with an abscess beneath the jaw from which tubercle bacilli were

obtained. This healed slowly while he was in the hospital and caused no general reaction during this time.

Discussion of case 11. Another example of the differentiation of the factors influencing red cell increase from those influencing haemoglobin increase is afforded by this case. The rise in reticulocytes and preponderance of blood formation which followed the administration of iron was accompanied by a well marked rise in red cells, which then tended to remain at a constant level as the preponderance of blood formation decreased. The haemoglobin, on the other hand, rose rather slowly during this period. At the time copper was given there occurred a second

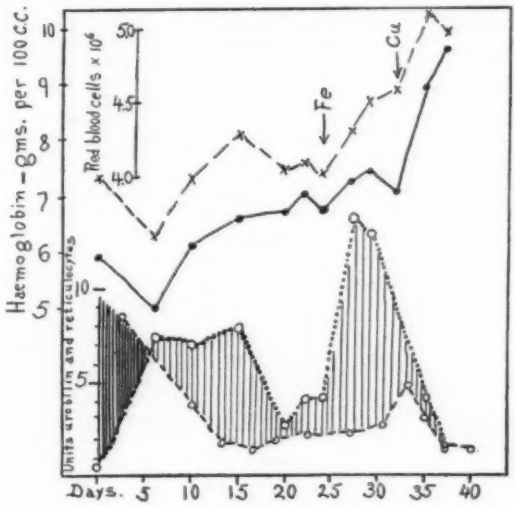

CHART VIII. (CASE 10)

rise in reticulocytes independent of the copper. This time both red cells and haemoglobin increased rapidly.

Case 12 (table 12). M. M. White. Male. Age: 12½ months The child was a twin, born at term, weighting 4 lbs. He had always been healthy and not subject to respiratory infections. He was breast fed only 9 weeks and then was given a cow's milk formula, supplemented by cod-liver oil and orange juice. The attempt had been made to give him vegetables; but these were poorly taken and often vomited. His mother thought that he had always been pale. The examination was negative, except for the systolic murmur that so often is present when the anaemia is as severe as this, and a slightly enlarged liver. The spleen was not palpable.

TABLE 7

J. S. Case 7

DATE	WT.	HGB.	R.B.C.	RETICULOCYTES	C.I.	TOTAL HGB.	DATE	UROBILIN EXCRETION		UNITS		
								Mgs. per day	Mgs. per day hgb.	Urobilin	Reticulocytes	
	kg.	*gms. per 100 cc.*		*per cent*		*gms.*						
1/29/30	8.5	9.8	5.5	1	0.64	63	28–31	85	1.3	3.4	1.4	
2/ 1	8.5	10.8	5.0	2	0.77	70	31–2/2	38	0.55	1.4	2.8	
3	8.5	10.1	4.7	3	0.77	65	2–5	10	0.15	0.4	4.2	
8	8.5	10.1	4.9	1	0.74	65	6–10	12	0.18	0.5	1.4	
12	8.5						10–13	42	0.68	1.7	—	
14	8.5	8.8	4.5	0	0.70	57	13–17	70	1.2	3.1	0	
18	8.5	8.2	4.0	1	0.72	53	17–22	32	0.61	1.5	1.4	
22	8.5	7.7		2	—	50	—	—	—	—	2.8	
26	8.5	8.9	4.7	5	0.68	57	22–28	32	0.60	1.5	7.0	
3/ 1	8.5	9.6	4.9	5	0.70	62	28–3/3	22	0.35	0.9	7.0	

TABLE 8

F. W. Case 8

2/14/30	7.4	9.7	5.1	<0.5	0.68	55	15–17	50	0.90	2.3	0.5	
18	7.0	8.8	4.4	1 ±	0.71	47	17–20	18	0.38	0.9	1+	
20	7.0						22–25	15	0.33	0.8		Crisis 2/20
2/26	6.9	10.4	4.5	1.5	0.83	55	25–28	15	0.27	0.7	2.0	
							3/4–6	20	0.36	0.9		
							6–8	32	0.56	1.4		
3/ 9	6.9	10.7		1 ±		57	8–10	33	0.57	1.4	1.4	

TABLE 9

J. S. Case 9

2/ 4/30	6.6	7.3	4.05	2	0.65	37	4–6	16	0.43	1.1	2.8	
10	6.5	7.9	4.1	1	0.70	39					1.4	General diet 2/9
14	6.7	7.6	4.37	5	0.62	39	11–14	16	0.41	1	7	Temp. normal 2/6
19	6.9	7.9	5.20	2	0.55	41	14–16	18	0.45	1.1		
2/24	7.2	7.4	—	—		40	19–22	23	0.56	1.4	2.8	
							—	—	—	—	—	

TABLE 10

H. H. Case 10

2/ 4/30	9.2	5.9	4.0	<0.5	0.53	41					0.5	
							6–7	125	3.4	8.5		
10	8.7	5.0	3.6	6	0.50	34						Temp. normal 2/10
14	8.9	6.2	4.0	5	0.55	42	13–15	63	1.5	3.8	8.6	
							16–18	30	0.70	1.7	7.0	
19	8.9	6.6	4.3	5.5	0.55	45	19–22	25	0.55	1.4		General diet
24	9.4	6.7	4.1	2	0.58	48	22–24	36	0.73	1.8	8.0	

TABLE 10—*Concluded*

DATE	WT.	HGB.	R.B.C.	RETICULOCYTES	C.I.	TOTAL HGB.	DATE	UROBILIN EXCRETION		UNITS		
								Mgs. per day	Mgs. per gm. hgb.	Urobilin	Reticulocytes	
	kg.	*gms. per 100 cc.*		*per cent*		*gms.*						
26	9.5	7.1	4.2	3	0.60	51	25–28	46	0.90	2.2	2.8	
2/28	9.6	6.7	4.1	3	0.58	49					4.2	Fe begun 2/28
3/ 3	9.6	7.3	4.3	10	0.61	53	3/2–5	45	0.85	2.1	14	
5	9.6	7.4	4.5	9	0.59	54	5–8	58	1.05	2.7	13	
8	9.7	7.1	4.6	—	0.55	52	8–10	100	1.9	4.8	—	Cu begun 3/8/
11	9.9	8.9	5.2	3	0.62	67	10–12	85	1.25	3.1	4.2	
3/13	9.9	9.6	4.8	—	0.71	72	12–14	50	0.69	1.7	—	
							15–17	53	0.73	1.8	—	

TABLE 11

P. M. Case 11

1/31/30	8.5	5.3	4.3	2	0.44	34	1/29–2/1	50	1.43	3.6	2.8	
2/ 3	8.5	5.3	3.9	1	0.48	34					1.4	
5	8.5	5.3	4.3	2	0.44	34	5–7	25	0.74	1.9	2.8	Fe begun 2/5
7	8.5	5.7	4.0	3	0.51	36					4.2	General diet 2/6/
9	8.6	5.6	4.4	6	0.45	36					8.6	
10	8.6						9–12	105	2.6	6.6		
13	8.6	6.3	4.8	6	0.47	41	12–15	70	1.7	4.2	8.6	
16	8.6	6.4	4.7	4	0.49	42					5.7	
19	8.7	6.6	4.8	3	0.49	44					4.2	
22	8.7	6.7	4.8	5	0.50	44	20–22	44	1.0	2.5	7.1	Cu begun 2/22
24	8.7	8.3	5.2	5	0.57	55	22–25	75	1.35	3.4	7.1	
2/28	8.7	10.0	5.6	4	0.64	66	25–28	51	0.77	1.9	5.7	

TABLE 12

M. M. Case 12

3/ 3/30	8.0	3.4	—	3		21					4.2	Fe begun 3/3/
5	7.8	3.8	3.0	3.5	0.45	23					5.0	General diet
6	7.6	3.9	3.2	7	0.43	22	4–8	85	4.0	10	10	
8	7.6	4.2	—			24					25	
9	7.6	5.0	3.1	18	0.58	29	8–12	45	1.8	4.5		
10	7.6	4.5	—			26						
11	7.7	5.9	3.8		0.55	34						
13	7.9	6.3	3.7	13	0.61	38	12–15	53	1.4	3.5	19	
16	7.9	6.9	4.3	13	0.57	41					19	
18	7.9	6.6	4.6	8	0.51	40	17–19	40	1.0	2.5	11	Cu begun 3/18
21	7.9	8.4	5.0	3	0.60	50					4.2	
23	8.0	9.1	—	1		55					1.4	
29	8.1	10.5	—			65						

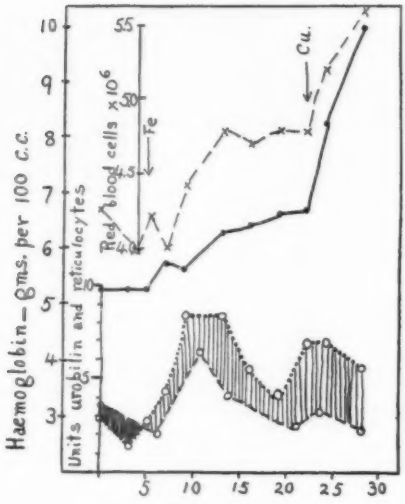

CHART IX. (CASE 11)

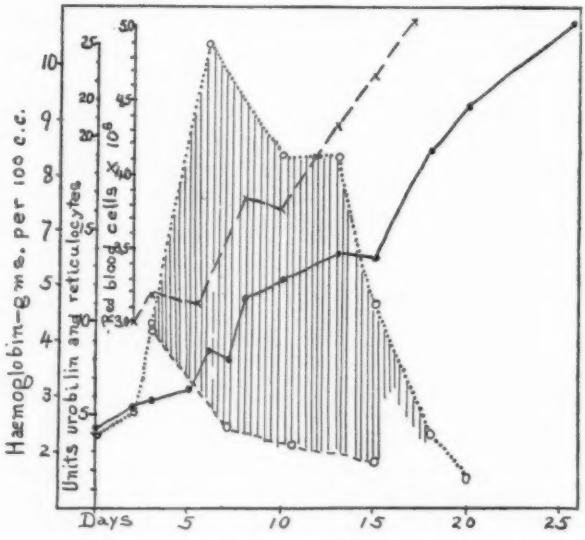

CHART X. (CASE 12)

Case 13 (table 13). L. M. White. Male. Age: 12½ months. This child was the twin of the preceding case. The history and physical examination were the same.

Discussion of cases 12 and 13. An examination of the charts in these two cases is most instructive, for these babies were similar twins, as nearly identical, pathologically speaking, as might well be. One (No. 12) was treated with iron alone, then with the addition of copper; the other (No. 13) was treated with iron and copper from the beginning. In No. 12 from the beginning of treatment there was

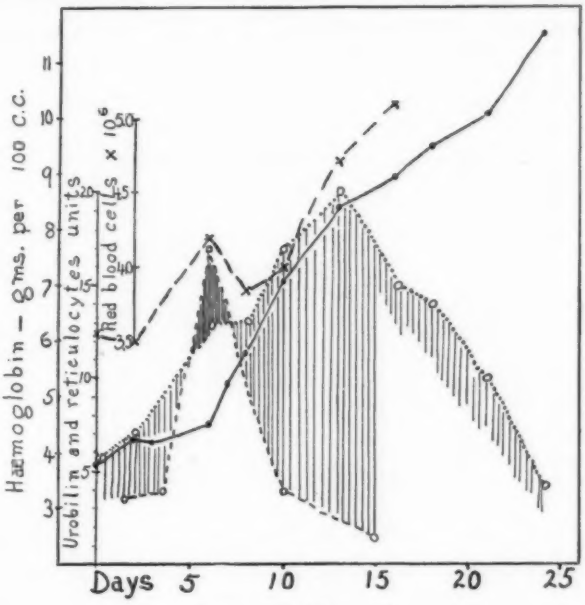

CHART XI. (CASE 13)

a marked preponderance of haemopoietic activity, and the red cells rose steadily. The haemoglobin, on the other hand, followed the course outlined in the previous paper as the average in cases treated with iron alone until copper was given, when there was a rapid rise in haemoglobin. In No. 13 for some reason there was an increase in the activity of blood destruction and here we see the red cells somewhat delayed in their rise while the haemoglobin increased steadily and rapidly from the time when the rise began six days after starting treatment. (This latent period is frequent in the case of the haemoglobin rise and was discussed in the previous paper.)

TABLE 13

L. M. Case 13

DATE	WT.	HGB.	R.B.C.	RETICULOCYTES	C.I.	TOTAL HGB.	DATE	UROBILIN EXCRETION		UNITS		
								Mgs. per day	Mgs. per gm. Hgb.	Urobilin	Reticulocytes	
	kg.	*gms. per 100 cc.*		*per cent*		*gms.*						
3/ 3/30	8.2	3.8	3.6	4	0.38	24					5.7	Cu and Fe begun 3/3
5	8.0	4.3	3.5	5	0.44	26	4–5	37	1.4	3.5	7.1	General diet
6	7.9	4.2	3.9		0.38	25	5–8	38	1.5	3.8	—	
9	7.7	4.5	4.4	9	0.37	26	8–10	175	6.7	17.	13	
10	7.7	5.3				31					—	
11	7.8	5.8	3.6	9	0.57	34					13	
13	8.0	7.1	4.0	12	0.63	43	11–15	65	1.5	3.8	17	
16	8.1	8.4	4.7	14	0.64	52					20	
19	8.1	8.9	5.1	10.5	0.63	55	17–19	33	.6	1.5	15	
21	8.2	9.4		10		59					14	
24	8.3	10.1		7		64					10	
27	8.3	11.5		3		72					4.2	

TABLE 14

W. B. Case 14

5/22/31	10.2	2.9	2.43	6	0.43	22	22–24	160	7.2	18	8.6	Milk and farina
24	10.2	3.2		6		25					8.6	Fe begun 5/23/
25	10.2	3.4	2.40	4	0.51	26	24–26	55	2.1	5.2	5.7	
27	10.2	3.8	2.98	7	0.46	29	26–29	50	1.7	4.3	10	
29	10.2	3.9		12		30					17	
5/30	10.2	4.9		10		38					14	
6/ 1	10.2	5.9		8		45	6/1–3	120	2.7	6.8	11	
3	10.0	5.9		6		45	3–6	30	.67	1.7	8.6	
8	10.1	7.6	4.34	4	0.62	58	8–11	60	1.05	2.6	5.7	
11	10.1	7.1		4		54					5.7	
13	10.1	7.5		2		57					2.8	
15	10.2	7.7	4.60	1	0.60	59	14–16	40	.68	1.7	1.4	Cu begun 6/15
16	10.2	8.6		1		66					1.4	
18	10.1	8.5	4.67	1	0.65	65					1.4	
22	10.2	9.5	5.00	1	0.68	73					1.4	

TABLE 15

B. R. Case 15

5/27/31	5.1	3.4	1.0	3	1.2	13	26–28	50	3.8	9.5	4.2	
5/29	5.0	3.6		4		14	28–30	41	2.2	5.5	5.7	
6/ 1/	5.0	4.5		16		17	1–3	30	1.7	4.4	23	
3	5.1	4.5	1.5	12	1.05	17	3–6	31	1.8	4.5	17	
8	5.0	5.5		10		21					14	
11	5.0	6.3		8		24					11	
13	5.0	6.6		8		25					11	
15	5.0	7.1		8		27	13–16	20	.75	1.8	11	
18	5.0	8.9		7		34					10	
22	5.2	9.7		5		37					7	

On the basis of the observations in the last six cases we may divide the blood forming process into two phases: (1) Haemopoietic activity, resulting in the formation of red cells, its extent indicated by the reticulocyte percentage; (2) "Haemoglobin synthesis," the activity of which is indicated by the slope of the haemoglobin curve, after taking into account the rate of "urobilin" excretion. While rises and falls in the red cell count appear to correspond quite closely with the preponderance of formation or destruction of blood as shown in the charts, the haemoglobin curve does not correspond so closely to changes in the reticulocyte count or "urobilin" excretion, but takes its course to some extent independently.

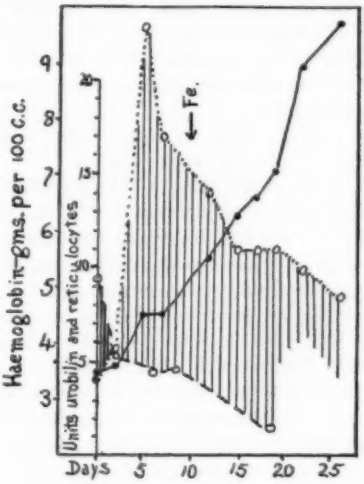

CHART XII. (CASE 15)

Administration of iron usually has an immediate effect on the reticulocytes, the percentage of which reaches a maximum on about the fourth to the seventh day. It has been found in some cases that iron has no effect on the reticulocytes; these cases fall principally into two groups: 1. Premature babies in the first few months of life; 2. Patients with active infections particularly those of a pyogenic nature. In these cases a cure of the anaemia is not to be expected. While administration of inorganic iron appears to have an immediate and a striking effect on "haemopoietic activity," copper, on the other hand, is followed by a rapid haemoglobin synthesis, without necessarily any preponderance of "haemopoietic activity."

Case 14 (table 14). W. B. White. Male. Age: 19 months. The child was born at term, weighting 7 lbs. He was breast fed 3 months, then given condensed milk until he was a year old. From the age of 1 year he received whole

cow's milk without any addition to the diet except orange juice and cod-liver oil. He was said to have had a "golden color" for the first three months, and to have been pale since that time. He had pneumonia at 5 months and was subject to colds. About ten days before his admission to the hospital he had some sort of an infection with abdominal pain and remained feverish up to the time of admission. On examination he had rickets; a moderate general glandular enlargement; the liver and spleen were both considerably enlarged; Wassermann negative; Tuberculin test negative.

Discussion of case 14. In this case there is again some doubt as to the origin of the anaemia considering the "golden color," the "repeated infections" and the "nutritional" factors, although it appears quite likely that the faulty nutrition was the important factor in the persistence of the anemia. It is probably that the high "urobilin" excretion at the beginning of the study was dependent on the infection at the time of admission.

Case 15 (table 15). B. R. White. Female. Age: 15 months. The family history had no bearing on the etiology of the anaemia.

The baby was born at the seventh month and weighed 2¾ pounds at birth. She was fed on a cow's milk mixture without cod-liver oil or orange juice up to her admission to the hospital. She had no illnesses, but underwent an operation for repair of hair-lip at 5 months. She also had a cleft palate. She developed poorly and was always pale. About two weeks before admission she developed the evidences of scurvy for which she was brought to the hospital. Wassermann and Tuberculin tests negative. (For blood findings and course in hospital see table.)

Discussion of case 15. This is the only case I have so far seen in which a change of diet alone has been followed by any such dramatic cure of the anaemia. Almost from the moment orange juice and vegetables were added to the diet the haemoglobin started to rise, and continued to rise until a normal value was reached. Iron was given, but as may be seen was probably superfluous.

DISCUSSION

The foregoing cases have been considered not from the point of view of the clinical pictures presented but from that of the mechanism of the development of anaemia. It is evident that anaemia must result when blood formation is unable to keep pace with blood destruction. What has been attempted here is to find out whether it is feasible to express the rates of blood formation and destruction in units that will allow a balancing of the opposing processes. That such a procedure is feasible is evident from the results as set forth in the charts and tables, and there has already been ample consideration of this point in discussing the individual cases. It must not be supposed that I am attempting to draw any conclusions as to the appearance of

the bone marrow from the percentage of reticulocytes. Such a conclusion would be entirely unjustified in the present state of our knowledge. I am considering the process of blood formation as a whole, as distinguished from the anatomical appearance of blood-forming tissue, without attempting an analysis of the process. Therefore, when I speak of hypoplastic process in the course of an infection, I use the term in a functional, not in an anatomical sense.

In the present state of this work generalization would be unwise. It certainly appears to be possible in the type of case reported here, namely, the post-infections-nutritional anaemia, to express the relation between blood formation and destruction quantitatively, using the reticulocyte percentage and "urobilin" excretion, respectively, as indices of the two opposing processes, but I have not found it possible to do so in the case of premature babies in the first four months of life, at least not with the same units. Another type of case in which failure would be inevitable is represented by a syphilitic baby of two months. The child was admitted with very severe congenital syphilis. The haemoglobin was under 20 per cent and the red cells under a million. The white cell picture, without going into details, was that often described as leukaemoid,—leukopenia with practically all the cells mononuclear of the lymphoid series, a large proportion of them immature. The urobilin excretion was very low, but 20 per cent of the red cells were reticulated and about 5 per cent nucleated. At autopsy the bone marrow was found to be almost completely aplastic, while, especially in the liver and kidneys, there were numerous islands of blood formation.

ETIOLOGY

We scarcely ever see a chronic anaemia in which there is only one etiological factor. Leaving out the unusual cases in which haemorrhage, poison, or such an agent as the X-ray plays a rôle, we have to consider three possible factors in every case that we see, namely infection, nutrition, and constitution. Constitution is a vague conception, and by it is meant a recognition of the fact that infancy is a period in which the organism is peculiarly susceptible to the agents causing anaemia, and that one child is more susceptible than another. Of course in some cases, as in certain types of aplastic or haemolytic

anaemia, the constitutional factor so outweighs the others as to dominate the picture, and lead to the designation of the anaemia as "primary." The so-called "physiological anaemia" of both full-term and premature infants in the first few months of life may be considered to be due to a temporary constitutional factor.

For practical reasons it is desirable to differentiate the factors causing the anaemia from those prolonging it. A knowledge of the factors which prolong an anemia is far more important for a plan of treatment. The original cause of the anaemia is often obscure and may be dependent on factors that have long since ceased to act:—an attack of pneumonia six months previously, prematurity, etc. After an attack of pneumonia in an otherwise healthy infant, the tendency is toward a spontaneous cure of the anaemia; the factors disturbing the normal balance between blood formation and destruction cease to act and equilibrium is again established at the normal level. During the infection it is virtually impossible to produce any therapeutic effect on the anaemia that will last more than a very short time. In some cases, after the pneumonia is over there is little tendency to a spontaneous recovery. In the case of J. S. (No. 9) who remained untreated, a year later the haemoglobin was still in the neighborhood of 6.5 g. per 100 cc. While this is probably an extreme case, it is true that many children do not recover after infection. It is in these cases that one sees the effect of a faulty diet in prolonging an anaemia that might otherwise have been quickly cured, and the term "nutritional anaemia" is as correctly applied to them as to those other cases in which a faulty nutrition is the only factor that can be found to explain the development of the anaemia. While mild infections alone probably will not cause any severe grade of anaemia they may help to prolong an anaemia already established, especially in infants whose diets are not entirely satisfactory or in those who have a diminished appetite for food other than milk.

Nutritional factor. What particularly is at fault in a diet is scarcely ever clear. In the last case I think we can say without question that here we have an example of an anaemia due to avitaminosis; possibly the lack of the antiscorbutic vitamin, the only clear case of the sort of this series. Two other cases (no. 2 and one whose history has been omitted) in this series had had long continued artificial feeding without

adequate orange juice or cod-liver oil. In neither of these did the change to an adequate diet alone have any influence on the anaemia. One other child (aged 11 months), reported previously, who had received no food but milk and no anti-scorbutic, and who had no signs of scurvy, did not show any increase in reticulocytes when orange juice was given, but had a very satisfactory increase as soon as iron was administered.

The oldest and perhaps the most firmly established idea of the nutritional fault is that the lack of iron in the milk is responsible. This is grounded on the observations of Bunge and Huguonenq, and depends to a large extent on the hypothetical presence of available stores of iron to explain why every baby fed on milk for more than a few months does not develop anaemia. This most plausible of hypotheses has much to commend it, but it must not be forgotten that the availability of iron stores belongs to the same category as the constitutional factor; a useful enough concept in general but one that can scarcely ever be strictly applied individually.

While the lack of iron in the diet is of the utmost importance to an understanding of many cases of "nutritional anaemia," undoubtedly in many other we have to look further than a mere lack of a building stone for haemoglobin. We find evidence of some other factor or factors in the behavior of the reticulocytes and "urobilin" excretion. In a severe infection such as pneumonia, the reticulocytes are often depressed and the "urobilin" excretion somewhat raised, as a result of the infection. As soon as the infection is over the state of affairs is altered, the reticulocytes rise somewhat, the "urobilin" excretion falls somewhat and all is set for recovery, which may take place spontaneously or only after the spur of inorganic iron has been applied. The rise in the excretion of "urobilin" in those cases without infection is difficult to understand. At first sight it would seem as if those who held to the idea of some toxic substance in the milk (such as fat) causing an increased haemolysis may be right. Further observations do not point to this as the correct explanation, however, for the "urobilin" excretion may decrease as the haemogoblin and red cells rise while the child is still on a milk diet. I have few cases to offer in which the diet remained milk alone while recovery from anaemia followed the use of inorganic supplements, but it must be borne in mind that the idea of

the toxic nature of milk has never been more than a somewhat plausible hypothesis without much evidence to support it.

Effect of iron and copper. The effect of inorganic iron is without question; it is the mechanism that needs analysis. The stimulating action of iron has long been known, long before the influence on reticulocytes was determined. The observations here merely confirm this effect. Two things are worth pointing out. First, that the reticulocyte rise occurs immediately after iron is given, not after the lapse of several days as in the case of adults, and the rise is greater than in the case of adults; second, that there is a possible parallelism between the extent of the rise in reticulocytes and the rapidity with which the red cells rise, a point that needs more confirmatory evidence. In the majority of cases there was a temporary rise in the urobilin excretion after iron was given, but this may be dependent on constipation which in itself tends to increase the amount of urobilin to be found in the stools.

The effect of copper is more difficult to prove. In a previous paper I attempted to do it by statistical means, and in some cases its influence on the haemoglobin curve can hardly be doubted. The material presented in this paper is not intended to be used as proof of the beneficial effect of copper, but only for a study of the mechanism of its action so that its limitations may be ascertained. Copper had no demonstrable influence either on the reticulocytes or on the urobilin excretion. The most striking result of its use is on the haemoglobin formation, although an effect on the red cells cannot be ruled out. As a result of the analysis of the process of recovery in individual cases, it seems as if iron affected principally that phase of haemopoietic activity that was concerned with the red cell increase, while copper affected chiefly haemoglobin formation with consequent tendency to an increased color index.

Nothing that has yet been done has shown that the addition of inorganic copper is essential to the cure of any case of anaemia. That it accelerates recovery in some cases at least can hardly be questioned. From the studies reported here I should be inclined to think that its chief use will be in those cases in which it is desired to raise the color index. Whether it will prove to be of use in the anaemias of older children or adults remains to be seen, but it must be borne in mind that

the blood of infants is more labile than that of older children or adults and that just as an anaemia is more easily caused in infants, so is it more rapidly cured. For this reason, such striking effects as I have occasionally seen in infants are not to be expected in older patients.

REFERENCES

(1) R. Elman, and P. D. McMaster: *Jour. Exp. Med.*, 1925, **41**, 503.
(2) H. Josephs: *Bull. Johns Hopkins Hosp.*, 1931, **49**, 246.

NECROSIS OF THE SPINAL CORD PRODUCED BY ELECTRICAL INJURIES[1]

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The author has become interested in spinal cord injuries involving the central portion of the cord and extending a considerable distance in a longitudinal direction, their mode of production and their development. This problem reaches its greatest importance in the study of the cavities produced in the cervical portion of the cord and in the brain stem in syringomyelia and syringobulbia. It is commonly held that syringomyelia is due to the development of a glial tumor which undergoes necrosis with the formation of a central cavity containing fluid. There is, however, considerable evidence that vascular injuries or traumata may produce similar changes. For example, a tumor in the medulla or pons, causing increased intracranial pressure, may lead to the development of a cavity in the central portion of the cervical cord having no connection with the neoplasm. It has been suggested that obliteration of the lumen of the anterior spinal artery by the pressure cone is responsible for this abnormality. These cavities are most common in the cervical portion of the cord, but often extend upward into the medulla. The cavity usually occurs in the region around the central canal, sometimes involving the central canal itself.

The central portion of the normal spinal cord is not of as firm consistency as the remainder. The areas just lateral and posterior to the central canal contain relatively few nerve cells or nerve fibers and are made up of glial cells and a meshwork of glial fibers which are readily invaded by any advancing lesion. Moreover, this is the least vascular portion of the spinal cord. The blood vessels enter the edges and only their terminal branches supply the central portion.

[1] This research was conducted with a fund provided by the Committee on Electric Shock.

The fluid in a syringomyelic cavity is often under considerable pressure. Indeed it is believed that it is only when the pressure of the fluid is increasing that the patients show advancing symptoms, and the most efficient method of treatment is the draining of this fluid into the subarachnoid space, leaving a permanent fistula. The reason for the development of increased pressure in the cavity is difficult to explain. It is possible that the cells of the wall actually secrete or that the cavity behaves after the manner of a retention cyst. As a result of the development of the large cyst the remaining structures are subjected to great strain and are flattened out on the surface of the cavity. The walls of the cyst are often surrounded by a great mass of glial tissue and the glial overgrowth may be the primary abnormality. On the other hand, the gliosis may be a response to the long-standing injury.

Holmes (1915) found that peculiar cavities were sometimes formed in the spinal cord of men following war injuries. They were dependent on the concussion or commotion effects produced by a missile which had struck some portion of a vertebra. These cysts were cylindrical or oval in cross section and extended for four or five segments on either side of the lesion. They were always situated in the dorsal columns of the cord except in one case in which they were found in a dorsal horn. The size was often considerable so that they were distinctly visible to the unaided eye. They contained a grayish or brownish gelatinous material, sometimes tinged with blood. The area on microscopic examination was found to be made of broken and degenerated fibers and a certain number of red blood cells. The contents existed under pressure, inasmuch as the unaffected parts around the cavities were compressed. Holmes believed that they were produced by a localized edema.

The author has recently produced peculiar cavities in the posterior columns of the spinal cord of rats by means of an electric current. A considerable number of rats were exposed to alternating or continuous electric circuits at different potentials, the contacts usually being made with the dorsal surface of the head and with the tail. All the animals were given ether before the experiment. The time that the current flowed was varied from that required to open and close the switch to several seconds. The results of this study have

already been reported in other places (Langworthy and Kouwenhoven, 1930 and Langworthy, 1930).

The hind-legs and posterior portion of the body were paralyzed in a large group of rats after contact with electric circuits. The paralysis was much more common after shocks from alternating circuits than after shocks with continuous circuits and there were other distinguishing features of the two groups. Weakness in the hind-legs in the rats shocked with continuous currents, even though marked directly

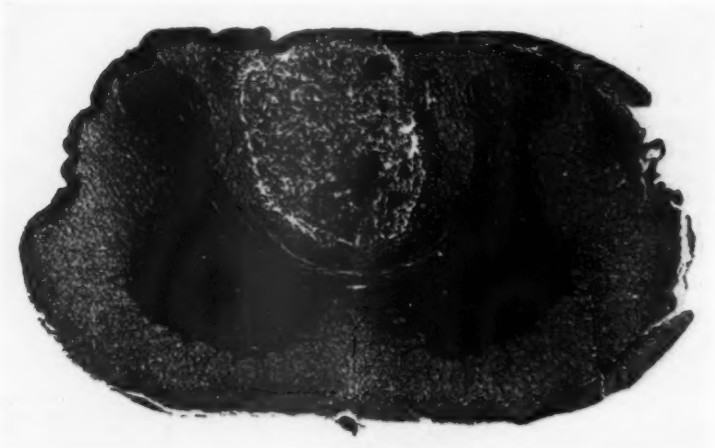

FIG. 1. TRANSVERSE SECTION OF THE SPINAL CORD OF A RAT STAINED WITH HEMATOXYLIN AND EOSIN, WHICH SHOWS THE CHARACTERISTIC LESION

after the injury, had a tendency to decrease rapidly or even to disappear entirely. Probably the weakness may be attributed to a temporary injury of the cells of the spinal cord. It is only the paralysis produced by contacts with alternating circuits that is to be considered here.

This paralysis was produced by contact with circuits at a wide range of voltages (18 to 1000). In some groups of experiments fifty per cent of the rats subjected to the current showed the paralysis and many of the animals which died immediately as a result of the

shock had probably developed the characteristic type of pathological change. As soon as these rats recovered from the acute effect of the shock and attempted to walk they dragged the hind-legs. No response to nocuous stimuli could be elicited from the hind-legs or tail a few hours after the injury. The subsequent behavior of the paralyzed rats was characteristic. After twenty-four hours the majority of the animals were incontinent and blood was found in large quantities in the urine. None of the animals would eat or drink. They showed no spontaneous activity and lay quietly for hours in any position in which they were placed. If disturbed, the anterior portion of the body was active. None of them could be kept alive for more than two or three days.

With experience it became possible to predict the animals that would be paralyzed immediately after the circuit was opened. Clonic twitchings of the hind-legs and of the lower back musculature and twisting movements of the tail were evidence of an advancing irritative lesion. This irritation was followed by a period of complete inactivity lasting much longer than in the uninjured animals. Then the paralysis was manifest approximately twenty minutes after the shock.

The central nervous system of all the rats injured with electric currents was studied both macroscopically and microscopically, and the spinal cords of the rats paralyzed after contact with the alternating circuit all showed one characteristic lesion. When the spinal cord was exposed in these animals it was always found to be abnormally soft. The posterior columns of the cord in the upper thoracic and cervical region were of a dull lavender color. Macroscopic transverse sections showed a lesion, usually in the posterior columns of the cord, which was distinctly visible to the eye. The characteristic change in the posterior columns is shown in figure 1.

The exact amount of the cord involved varied greatly in different cases. Usually the lesion spread through the entire posterior column area and extended for a considerable distance in a cephalo-caudad direction. It was then held in check by the gray matter of the cord which prevented its further spread. If the injury then continued to grow, it broke through the gray matter at its narrowest point, that is, in the region of the central canal, first spreading into the central canal

itself and then into the anterior columns of the cord. In this way the cord sometimes became bisected by the lesion and complete necrosis followed. These injuries never occurred primarily in the gray matter of the cord.

When the contents of the necrotic areas are studied microscopically, they are found to contain relatively few red blood cells, although there are enough to give the dorsal surface of the cord a lavender color in the macroscopic material. Numbers of leucocytes are present in the cavity but most of the area is filled with fat and amorphous débris. Apparently considerable fluid was accumulated and it is probable that the size of the cavity is due in large part to the development of a local edema. When the lesion is localized in the posterior columns, the central canal of the cord is often flattened out showing that the fluid in the cavity must have existed under considerable pressure.

At first it was thought that the lesion was primarily a vascular one, due to rupture of the small artery in the dorso-medial septum of the cord. Two possible explanations for this type of vascular injury may be advanced. When the body makes contact with an alternating electric circuit, all of its musculature contracts very suddenly and violently. The trunk of the rat is sharply flexed. It is possible that this sudden flexion of the body is responsible for the rupture of the blood vessel. If this were the case, it would seem probable that the accident would be commoner in older rats with existent damage of the arterial walls. This is not true, for paralysis occurs as often in young rats as it does in older ones.

The other explanation upon a vascular basis has to do with the sudden marked rise of blood pressure following electric shocks. Urquhart (1927) has been able to demonstrate that blood is collected in the veins during the application of the current, and following the opening of the circuit the sudden flow of this blood into the heart and arteries produces a rise in blood pressure which subsequently slowly drops. Urquhart believed that this rise is responsible for the small hemorrhages which frequently occur in the brain and it may also account for the spinal cord damage. If the injury to the spinal cord were caused by rupture of a blood vessel due to increased blood pressure, it would scarcely seem possible that the lesion would inevitably occur in the posterior columns in the upper thoracic region. Moreover,

rupture of an artery the size of the one in the dorso-medial septum would probably produce much more extensive bleeding than that actually present. Indeed sections of the cord show very localized changes in most cases. The number of red blood cells in the necrotic area is not as great as one would find if bleeding had produced the damage; instead, groups of red blood cells are scattered in the areas filled with fat globules.

Another possible cause of the injury is the direct action of the current upon the cord, producing an injury of the fibers in the posterior columns. Perhaps the best argument supporting this hypothesis is the following. Paralysis is most common when the current pathway is from head to tail and occurs much less often when the contacts are made between fore-legs and hind-legs. If the current passes from one hind-leg to the other, no paralysis ever appears. When the circuit makes contact with the head and tail of the rat, the bulk of the current traverses the vertebral column and spinal cord. The lesion occurs in the thoracic or narrowest portion of the cord where the concentration of the current would be greatest.

It is improbable that histological studies will throw further light upon the development of the paralysis. The rats cannot be kept alive for more than two or three days after the accident; this does not give time for the fat globules to be broken down to the point where they stain differentially with Scharlach R and Neutral Red. The microscopic picture is essentially the same in the rats that were killed as soon as the paralysis was manifest as in cases in which the animals had survived for hours.

It is interesting to correlate these abnormalities in rats with similar changes produced in man after a different type of trauma. In both instances the lesion involved the posterior columns of the cord. The cavities contained relatively few red blood cells but rather fat droplets and débris. They were filled during life with fluid under pressure. The lesion was most common in the upper thoracic and cervical region. It must be concluded that the posterior columns are particularly susceptible to lesions of this kind and the more so in the upper thoracic and cervical portion of the cord.

Unfortunately, the rats could not be kept alive long enough to permit the ultimate fate of these cavities to be studied. It is possible

that glial proliferation might have occurred at the edges and the necrotic area remained as a permanent cyst. In certain cases of syringomyelia there is a definite history of trauma to the region of the vertebrae.

SUMMARY

Anesthetized rats were subjected to alternating electric circuits at different potentials (18 to 1000 volts), the contacts being made with the dorsal surface of the head and tail. Many of the animals thereafter developed a complete paralysis of the posterior portion of the body with incontinence. It is thought that the injury was caused by the direct action of the current upon the spinal cord. The lesion, in general, remained confined to the posterior columns, although sometimes the whole cord became necrotic. The cavity contained relatively few red blood cells but many fat droplets and some amorphous débris. Similar cavities develop in the spinal cord of man as concussion effects after war injuries. The posterior columns appear to be particularly susceptible to injury, while the gray matter of the cord offers considerable resistance to the spread of the lesion.

BIBLIOGRAPHY

HOLMES, GORDON, 1915. Spinal injuries of warfare. I. The pathology of acute spinal injuries. Goulstonian Lecture, *Lancet*, p. 769.

LANGWORTHY, O. R., AND W. B. KOUWENHOVEN, 1930. An experimental study of abnormalities produced in the organism by electricity. *Jour. Indust. Hygiene*, **12**, 31.

LANGWORTHY, O. R., 1930. Abnormalities produced in the central nervous system by electrical injuries. *Jour. Exp. Med.*, **51**, 943.

URQUHART, R. W. IAN, 1927. Experimental electric shock. *Jour. Indust. Hygiene*, **9**, 140.

ACUTE PNEUMOCOCCAL NEPHRITIS

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The most familiar examples of acute nephritis are those which occur in association with some form of streptococcal infection, and it has been assumed for a long time, with but little direct experimental evidence, that the lesions in the kidneys represent the effect of toxins produced by these bacteria.

The recent studies of Longcope (1) especially have shown that the onset of acute nephritis, particularly in adults and during adolescence, is associated very frequently with infection of the tonsils or cranial sinuses with haemolytic streptococci. All of the streptococci from the cases investigated by Longcope formed toxic substances in broth cultures. Filtrates of these cultures produced inflammation when injected into the skin. It has been suggested, however, that in the presence of infection with haemolytic streptococci the appearance of nephritis may depend upon the development of allergic hypersensitivity, and Lukens and Longcope (2) have shown that "acute glomerulitis" is produced much more frequently in rabbits sensitized to haemolytic streptococci than in normal rabbits when dead haemolytic streptococci are injected into the renal arteries of these animals.

The subacute nephritis which commonly develops during the course of bacterial endocarditis due to the streptococcus viridans in also familiar, and Rich, Bumstead and Frobisher (3) obtained filtrates from broth cultures of Streptococcus viridans containing toxins which produced haemorrhagic glomerular lesions when injected intravenously into normal rabbits.

There is little detailed information to be found in the literature concerning nephritis depending upon infection with bacteria other than streptococci. It is recognized that nephritis does occur with severe pneumococcal infections (MacCallum (4)). In 1884 Ernst (5), when he suggested that bacterial infection was the cause of acute nephritis,

described two cases associated with pneumonia, while Councilman (6), in 1897, describing the kidneys in acute nephritis, recognized the frequency with which it accompanies such pneumococcal infections as endocarditis, compared with its rarity in pneumonia. Definite information concerning pneumococcal nephritis is scanty, however, and we wish, therefore, to describe the gross and microscopical appearance of the kidneys in acute nephritis accompanying infection with pneumococci.

Of particular interest are, first, the frequency with which pneumococcal nephritis occurs and the circumstances under which it is seen; secondly, the nature of the lesions in the kidneys and their manner of production; and finally, the correspondence between nephritis occurring during infections and that produced experimentally by means of pneumococcal toxin.

From the investigation of the material described below it appears that acute nephritis of considerable intensity occurs fairly often (9.5 per cent in this series of cases) in young infants with pneumococcal infections such as empyema, organizing pneumonia, pericarditis, otitis media, and meningitis. So far as we have been able to find from the literature, little attention has been given to the changes in the urine, to kidney-function tests, or to changes in the chemical constituents of the blood which may occur during these chronic forms of pneumococcal infection. None of the cases of acute nephritis in the infants here described were recognized clinically, although it is agreed that in children acute nephritis accompanying infectious diseases may not be recognized unless the urine is studied (7), since the symptoms of nephritis may be overlooked in the presence of those of the primary infection. The changes in the kidneys of these infants are fresh in each instance, but the character and extent of the lesions is such as to leave no doubt that other similar cases would be accompanied by very definite alterations in the urine, blood chemistry, and kidney-function tests.

In older children and adults, in this series of cases, although small or moderate numbers of isolated lesions occurred in the glomeruli and tubular epithelium in many of the kidneys (76.8 per cent of the cases in this series), no example of acute diffuse nephritis was found.

Concerning the character of the lesions in acute pneumococcal

nephritis, it may be said that in the affected kidneys all of the changes are present which occur in any acute nephritis. It may be well here to repeat that in acute nephritis these include not only damage of the glomerular capillaries, but every degree of injury and destruction of the glomerular and tubular epithelium (MacCallum (8)). Fahr (9) names streptococci and pneumococci as the commonest causes of acute glomerular nephritis, and according to Aschoff (10), pneumonia is one of the principal causes of pure acute glomerular nephritis. Both authors, however, in discussing the causes of tubular nephritis point

TABLE A

GROUP	NUMBER OF CASES	PERCENTAGE OF TOTAL CASES	AGE OF PATIENTS	DURATION OF PNEUMOCOCCAL INFECTION	LESIONS IN KIDNEYS
I	52	54.7	46.1 per cent children	10 days or less in 73.1 per cent; 2 weeks or more in 26.9 per cent	Cloudy swelling in all. Other lesions in 30
II	34	35.7	56 per cent children	10 days or less in 37.5 per cent; 2 weeks or longer in 62.5 per cent	Changes intermediate in degree between those in Groups I and III
III	9	9.4	All infants	10 days or less in 27.2 per cent; 2 weeks or longer in 72.7 per cent	Acute nephritis. See Table B

out the changes in the tubular epithelium which occur in the kidneys during infections with pneumococci, and Aschoff gives the toxins of cholera, diphtheria, typhoid bacilli, and of pneumococci, along with such inorganic poisons as bichloride of mercury, as causes of tubular nephritis. In the cases of acute nephritis described below, the lesions in the epithelium of the kidneys are pronounced. Similar changes are found in the epithelial cells, however, in acute nephritis of infancy caused by infection with other bacteria (Streptococci and B. influenzae).

The glomerular lesions in some of the kidneys of the infants with pneumococcal nephritis are not as severe as is the damage to the epithelial cells, and this corresponds with the results obtained

when normal rabbits are given pneumococcal toxin. The lesions which occur in the glomeruli of the infants, however, are identical in character with those found in any acute nephritis of bacterial origin (table B).

AUTOPSY NUMBER	DURATION OF SYMPTOMS	GROSS APPEARANCE OF KIDNEYS	EVIDENCE OF INJURY TO GLOMERULI					
			Swelling, necrosis and regeneration of glomerular epithelial cells	Hyaline thickening of capillary basement membrane and of Bowman's capsule	Fibrin and hyaline thrombi	Fibrin exudate in glomerular capsules or tubules	Blood in glomerular capsules or tubules	
8370	2 days	Cortex swollen. Glomeruli conspicuous	0	++	+++++	+++	0	++
9619	3 weeks	Swollen, pale. Many haemorrhages in cortex	++	++	++	Occasional	+++	+
10209	2 weeks	Pale, swollen. Many haemorrhages. One small infarct	+	+	++	Occasional	+	++
10315	2 weeks	Soft, swollen	++	++	+++	Occasional	Occasional	++
10327	2 weeks	Swollen. Yellow opacities. Haemorrhages in cortex	++	++	Occasional	Occasional	++	+
10556	4 weeks	Cortex pale yellow	+	+	Occasional	Occasional	0	++
10576	2 weeks	Cortex swollen	+	+	++	0	0	++
10626	3 weeks	Cortex swollen, soft and yellow	+	+	+	0	0	++
10675	4 days	Described as normal in the gross	0	+	++++	Occasional	Occasional	++

That nephritis in these pneumococcal infections is caused by a toxin directly affecting the kidneys is indicated by the close correspondence between the lesions in the kidneys of the infected infants and those in

the kidneys of rabbits given pneumococcal toxin. Experimentally, the toxin produces in normal rabbits all the lesions of acute and subacute nephritis (11). Allergic sensitivity is not required, therefore, for the action of this bacterial poison on the kidney, and it may be said

	CHANGES IN RENAL EPITHELIUM						OTHER LESIONS				
Blood in glomerular capsules or tubules	Colloid transformation	Fresh necrosis of cells	Casts in tubules	Calcification of necrotic epithelium	Regenerating tubular epithelium	Wide tubules with flat epithelium	Inflammation with P.M.N. leucocytes in glomerular tufts, capsules or tubules	Fluid exudate with or without mononuclear leucocytes in interstitial tissue	Fibrin thrombi in capillaries between tubules	Thrombi in arterioles	Minute infarcts in renal cortex
0	+++	+	++	0	0	+	0	0	++	+++	0
+++	++	++	++	+	+	++	+++	0	Occasional	0	0
+	++	+	++	0	0	+++	Occasional	+	0	Occasional	+
Occasional	+	+	++	0	+	+++	0	++	0	0	0
++	+	++	++	+	++	+++	0	++	Occasional	0	0
0	++	+++	+++	+++	+++	+++	++	+	0	0	0
0	++	+	+	+	+	+++	0	++	0	0	0
0	+	+++	+	+	Occasional	Occasional	+	0	+	+	0	0
Occasional	+	0	+	+	0	0	+	0	0	+	Occasional	0

here that in order to produce pneumococcal nephritis in allergic animals, slightly immunized, it has been necessary to use much larger doses of toxin than in normal animals which are not allergic.

MATERIAL AND RESULTS

Microscopical sections of 95 kidneys have been studied. These represent all of the examples of lobar pneumonia, organizing pneumonia, empyema, pericarditis, endocarditis, and meningitis of pure pneumococcal origin among four thousand autopsies. Other pneumococcal infections of similar nature in which bacteria were concerned besides pneumococci, or where there were other agents capable of injuring the kidneys, have not been included. The kidneys of lipoid nephrosis, often associated with infection by pneumococci, have also been omitted from these studies.

The microscopical sections were stained with haematoxylin and eosin. For the demonstration of colloid drops in the renal epithelium, and of fibrin in the thrombi and exudate, Weigert's stain, copper haematoxylin, and Mallory's phosphotungstic acid haematoxylin were used. Changes in the basement membrane connective tissue of the glomerular capillaries were clearly demonstrated by the use of the Mallory-Heidenhain azan-carmin stain as recommended by McGregor (12).

The gross descriptions of the kidneys given in table B are taken from the autopsy protocols. The gross specimens were not available for examination.

The pneumococci were cultured and typed either from sputum and blood during life, or from the heart's blood and from organs at autopsy, or, as was usually the case, both during life and at autopsy. Five of the nine infants with acute nephritis had otitis media in addition to their other pneumococcal infections. Cultures were made from the ears in none of these five, and it has not been possible to make microscopical studies. In two of them pneumococcal meningitis was present, and in these the otitis media was almost certainly due to infection with pneumococci. It was probably of pneumococcal origin in the other three.

The other data, the duration and location of the infections, the age of the patients, and the changes in the urine are based on clinical histories and autopsy records. In the infants with nephritis generally only one examination of the urine was recorded.

After tabulating the injuries found in the kidneys three groups have been separated according to the severity of the damage (table A).

The first group comprises 52 cases (54.7 per cent of the kidneys studied). These kidneys show the least damage. There is considerable cloudy swelling in all of them. Definite injury to the glomerular capillaries (thrombi or haemorrhage), or severe injury of the epithelium (colloid drops, necrosis, calcification) have been found only occasionally in 30 cases in this group (31.5 per cent of those studied). The smallest percentage of children, as compared with adults, and the infections of shortest duration are represented in this group. Here also are most of the examples of uncomplicated lobar pneumonia.

In the second group, with injuries in the kidneys intermediate in degree between those found in the kidneys in groups I and III, there are 34 cases (35.7 per cent of the 95 kidneys). Children are more numerous in this group than in the first, and the infections, wherever located, are on the whole of longer duration than the ones in the first group. Thrombi within the glomerular capillaries, haemorrhages into tubules, and more marked changes in the epithelial cells than cloudy swelling alone (colloid drops, necrosis, calcification) occur more often in the kidneys in this group than in those of the first. The changes are not diffusely scattered, however.

The third group is composed of 9 infants with acute diffuse nephritis. The average duration of the pneumococcal infections in these infants is considerably longer than in the patients in the other groups. In two of them, however, (Autopsy No. 8370 and No. 10675) both with otitis media of unknown duration and meningitis, the symptoms of meningitis were of short duration, two and four days, respectively. The lesions in the kidneys of these two are correspondingly fresh (table B), consisting especially of very numerous thrombi within the glomerular capillaries, and early alteration in the tubular epithelium.

A short summary of each of the cases of acute nephritis is given below. The gross appearance of these nine kidneys, and the general character of the microscopical changes in them are described, and are summarized in table B.

CASE HISTORIES

Autopsy No. 8370. Colored female infant, 5 months old. Symptoms of meningitis for two days. Urine: no record. Anatomical diagnosis: Otitis media, meningitis (Pneumococcus Type III), acute nephritis.

Autopsy No. 9619. Colored male infant, 16 months old. Symptoms for two weeks. The urine contained albumin ++++, casts and leucocytes. Anatomical diagnosis: Otitis media, lobular pneumonia, empyema (Pneumococcus Type II), acute nephritis.

Autopsy No. 10209. Colored male infant, 22 months old. Symptoms for three weeks. The urine contained albumin ++++, and many casts. Anatomical diagnosis: Otitis media, organizing pneumonia (Pneumococcus Type III), acute nephritis.

Autopsy No. 10315. Colored male infant, 3 months old. Symptoms for two weeks. No record of urinalysis. Anatomical diagnosis: Osteomyelitis and meningitis (Pneumococcus Type IV), acute nephritis.

Autopsy No. 10327. White female infant, 18 months old. Symptoms for two weeks. The urine contained albumin +++, casts and leucocytes. Anatomical diagnosis: Otitis media, lobular pneumonia, empyema, pericarditis (Pneumococcus Type II), acute nephritis.

Autopsy No. 10556. Colored female infant, 3 years old. Symptoms for four weeks. The urine contained albumin +++, casts and leucocytes. Anatomical diagnosis: Pneumonia, empyema, peritonitis (Pneumococcus Type I). Acute nephritis.

Autopsy No. 10576. Colored female infant, 14 months old. Symptoms for two weeks. No record of urinalysis. Anatomical diagnosis: Pleurisy and pericarditis (Pneumococcus Type I or IV), acute nephritis.

Autopsy No. 10626. Colored male infant, 4 months old. Symptoms for three weeks. The urine contained albumin ++. Anatomical diagnosis: Empyema and pericarditis, (Pneumococcus Type III), acute nephritis.

Autopsy No. 10675. White female infant, 8 months old. Symptoms for four days. The urine contains albumin +. Anatomical diagnosis: Otitis media, and meningitis (Pneumococcus Type IV), acute nephritis.

GROSS AND MICROSCOPICAL APPEARANCE OF THE KIDNEYS

In the 9 cases of acute nephritis (table B) in the gross the kidneys are swollen and soft, with wide bulging cortex. They are generally pale, dull yellowish in color. Sometimes minute yellow opacities are seen, and small haemorrhages are found in varying numbers. In some kidneys, when there are many glomerular capillaries filled with thrombi, the distended glomeruli are conspicuous on the surface as red dots, and may be mistaken for minute haemorrhages.

In the microscopical sections changes are found in the interstitial tissue, in the blood vessels, particularly in the glomerular capillaries, in the epithelial cells.

The softness and swelling of the kidneys is partly due, at least in

some of the cases, to exudate of fluid into the interstices of the organs. The tubules therefore may appear to lie loosely separated from each other, and the connective-tissue fibers between the adjacent tubules are in the same way spread apart. There is no fibrin to be stained in this exudate, and only occasionally are found a few large mononuclear leucocytes and lymphocytes, although sometimes such leucocytes may be quite numerous in the vessels between the tubules.

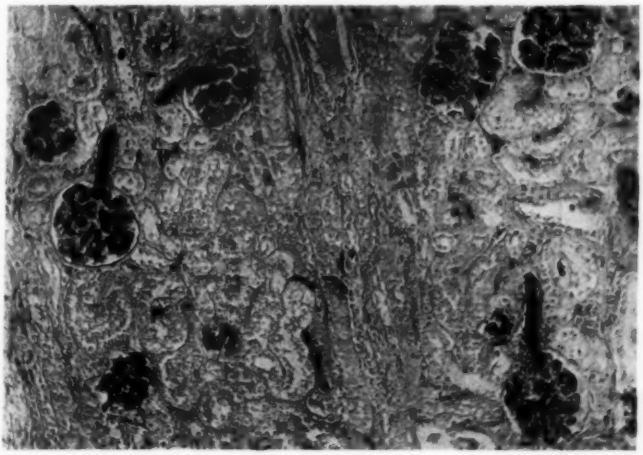

FIG. I. Autopsy No. 8370. Weigert's fibrin stain. Thrombi in glomerular arterioles and in capillaries.

The damage to the glomular capillaries, and to other blood vessels in the kidneys, which is described in more detail below, leads to the formation of fibrin thrombi within them. After a time the thrombi become hyaline in appearance. In the glomeruli they may be found in one or more capillary loops, but commonly many of the capillaries in a glomerulus are occluded, and in some kidneys very numerous glomeruli are found throughout the sections with most of their capillaries occluded by fibrin or hyaline thrombi, the glomerular tufts filling the capsular spaces (fig. I).

Fibrin and hyaline thrombi may also be found in some of the kid-

neys within the capillaries between the tubules. Usually (table B) they have been present in the kidneys in which thrombi in the glomerular capillaries were found to be numerous, and in the cases in which they are found, the thrombi in the glomerular capillaries are more numerous than those in the intertubular capillaries. No haemorrhages into the interstitial tissue have been seen associated with these capillary thrombi.

In 3 of the 9 cases similar fibrin and hyaline thrombi are present in pre-glomerular arterioles, and in one of these (No. 8370), where nearly every glomerulus is filled with capillary thrombi, the thrombi in the pre-glomerular arterioles are frequently continuous with those in the glomerular capillaries. In one case (No. 10209) a thrombus in a larger arteriole has led to the formation of a small infarct in the cortex, about 3 mm. in diameter.

In the glomeruli, and in other vessels, the thrombi evidently represent fresh lesions, certainly in those instances in which fibrin threads can be stained. The age of the thrombi, however, is not easy to determine, but that they are of some standing is shown by the presence of fibrin in the exudate within the corresponding tubules in the kidneys, and by the small infarcts occasionally associated with them. Furthermore, in rabbits with nephritis produced by means of pneumococcal autolysate, killed and autopsied promptly, similar thrombi are found in the glomerular capillaries. This shows clearly that, in rabbits at least, they are not postmortem clots.

Haemorrhages into the glomerular capsules and into the tubules have been found in considerable numbers in the kidneys of three of the cases (fig. II), occasionally in two, and none were present in the remaining four kidneys. Experimentally, the same variation in the haemorrhagic character of the nephritis occurs when rabbits and dogs are given pneumococcal toxin. The kidneys of some of the animals may be sprinkled with haemorrhages. In others none can be found even after careful search under the microscope.

Other alterations indicating injury to the glomeruli are found especially in the epithelium covering the capillary loops, and in the connective tissue of the capillary basement membrane and of Bowman's capsules.

The epithelial cells of the glomeruli, like those lining the tubules,

often contain colloid droplets. These are usually quite small, but are variable in size.

The glomeruli often appear to contain an increased number of cells, some of which, in the cases here described, are only infrequently polymorphonuclear leucocytes within the lumina of capillaries. One sees large glomeruli with very numerous large clear swollen-looking nuclei. In general, in nephritis, these cells are usually described as proliferat-

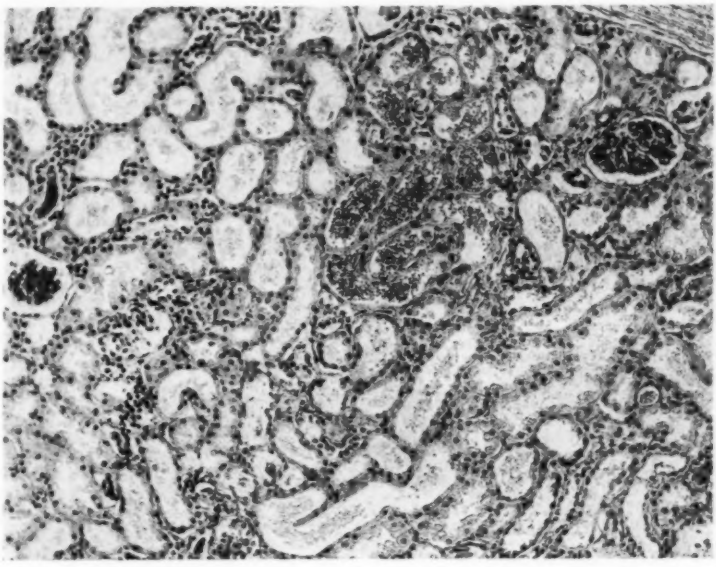

FIG. II. Autopsy No. 10327. Haematoxylin and eosin. Haemorrhage into tubules. Flat, vacuolated epithelium.

ing capillary endothelium or glomerular epithelium. In these cases of pneumococcal nephritis, the azan-carmin stain shows clearly that the majority of the nuclei concerned lie outside the capillary basement membrane, and it would seem therefore that many of them represent regenerating epithelial cells.

In addition to this change in the cells of the glomeruli, and to the presence of colloid drops within them, there is more severe injury, and the pyknotic fragments of nuclei of necrotic cells can be recognized.

The changes in the basement membranes both of glomerular capillaries and of Bowman's capsules can be seen even in the sections stained with haematoxylin. The connective tissue of these structures becomes thick and quite hyaline in appearance. Sometimes there is actual necrosis, especially of the basement layer of Bowman's capsule, and here there may be linear fragmentation and the collection of

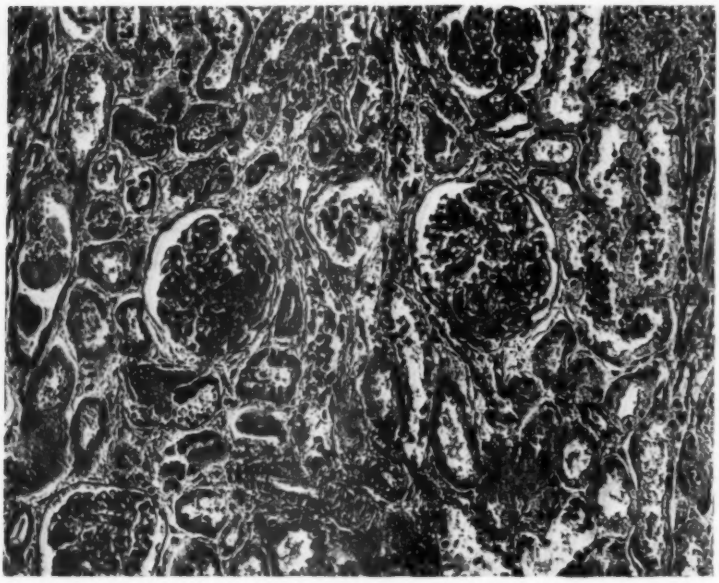

FIG. III. Autopsy No. 9619. Haematoxylin and eosin. Blood and necrotic cell casts in tubules. Thrombi in glomerular capillaries. Necrosis, swelling and fragmentation of Bowman's capsules.

pyknotic nuclear fragments in the crevices between the separated fragments.

Other alterations in the glomeruli are represented by adhesions between capillary loops and between the latter and Bowman's capsule, and also by glomeruli which show further stages of organization (fig. III). Crescents have not been found in large numbers. Their scarcity indicates evidently that the nephritis is not of long standing.

The changes in the epithelium, which are especially easy to see in the cells of the convoluted tubules, are marked. The cells show various kinds of injury. Those least injured have the granular appearance of cloudy swelling. In most of the kidneys droplets of colloid-like material are found in the cells of the convoluted tubules, often in large numbers of tubules. When present in small numbers within a cell the nucleus of the cell generally appears normal. Often, however, the entire cytoplasm of a cell, or of all the cells seen in a cross-section of a tubule, is converted into numerous globules of this clear, hyaline, colloid-like material. The nuclei of these cells are often pyknotic, or they may show another change characteristic of dying cells, namely, karyolysis. It seems that these cells are probably necrotic. At least the drop-like fragments of cytoplasm pass into the lumina of tubules where they may be found as casts. Other necrotic epithelial cells, with the more usual staining characteristics typical of coagulative necrosis, have been present in varying numbers in all of the kidneys in this group (table B).

In most of these kidneys there is little or no collection of polymorphonuclear leucocytes either in the glomeruli, in their capillaries, or within the tubules. In some, however, they are numerous, especially within tubules, associated with necrotic epithelium. Pneumococci are not found along with them. Concerning the degree of inflammation which may be found in the kidneys in any acute nephritis, it may be said that there is great variation. The "capillaritis" of the glomeruli described by Fahr as the essential lesion in acute nephritis may be very slight. This is true of acute streptococcal nephritis, and also of pneumococcal nephritis, whether occurring during infections with pneumococci, or produced experimentally in rabbits with pneumococcal toxin. The explanation of this variation is not clear. It may lie in the differences in the extent to which the tissues become sensitized during infection, differences, that is, in the degree of allergy which may be present. The experiments of Lukens and Longcope referred to above (2) have shown that, when haemolytic streptococci are injected into the renal arteries of rabbits, the resulting inflammation in the glomeruli is more marked in those of animals sensitized to haemolytic streptococci than in the glomeruli of non-sensitized rabbits. Since it is known that the lesions which develop in the tissues of aller-

gic individuals following introduction of antigen differ from those in non-sensitized tissues in the more marked degree of injury and inflammation which develop in the allergic (13), it is to be expected that necrosis produced by bacterial toxins in the kidneys of allergic individuals will be accompanied by more intense inflammation than that which follows the destruction of tissues which are not allergic.

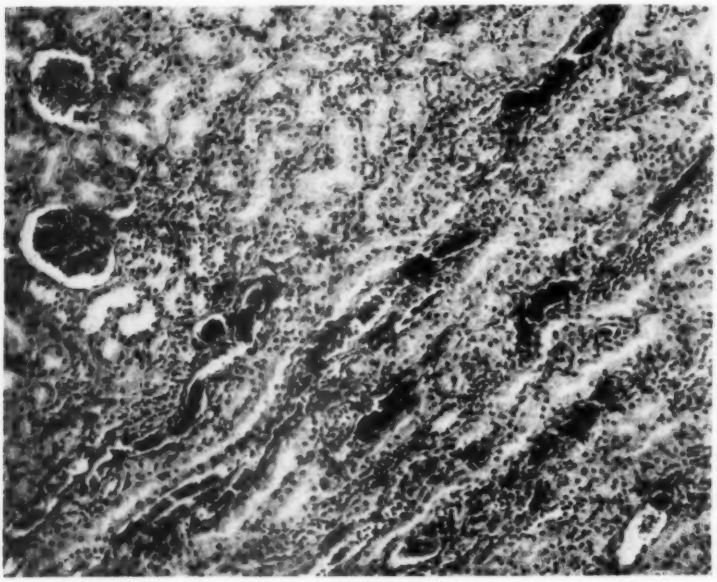

FIG. IV. Autopsy No. 10556. Haematoxylin and eosin. Calcified necrotic tubular epithelium. Leukocytes in a few tubules.

The necrotic epithelial cells frequently become calcified, especially those of the tubules within the cortical rays. At first, with the deposit of calcium, the dead cells stain purplish-red with haematoxylin and eosin. Later the calcified necrotic cells stand out on account of their deep blue color. They may be found in small groups lying within tubules *in situ* against the basement membrane, or a considerable portion of the epithelium of tubules may be necrotic and calcified for a long distance (fig. IV).

There is another striking alteration of the epithelium, both in that of the glomerular tufts and also in that of the tubular epithelium. This is due to a curious change whereby the cells become quite flat in character because there is a great loss of substance from each one. Consequently the tubules especially, and the glomerular capsules also, become very much widened. The material comes to lie within the glomerular capsules and tubules, at first in the form of coarse pink-staining granules. According to Jackson (14) these granules are converted into hyaline casts. The nature of the process which reduces the epithelial cells to their flattened form may be easily seen. It has been well described by Jackson, and consists, briefly, in the appearance of vacuoles within the cytoplasm of the cells. These vacuoles may be found as bulbous projections pointing into the lumina of the tubules. They rupture, and granules of cytoplasm, along with fluid, are extruded into the tubules. It is, apparently, largely on account of this alteration of the tubular epithelium, the wide lumina of the tubules being filled with fluid and granular particles of cytoplasm, that the kidneys are so soft and swollen in the gross. It seems quite probable, too, that some of the albumin which appears in the urine escapes through the rupture of the vacuoles described as occurring in the altered tubular epithelium.

Material fixed in formalin has been available in only three of these cases. The kidneys of these three, when stained for fat with Scharlach R, show finely divided fat particles in small numbers in a few cells of scattered tubules, occasionally within cells of glomerular tufts, and within the endothelial cells of capillaries between the tubules.

Bacterial stains of the kidneys of these infants have shown the presence of pneumococci in the capillaries of all of them excepting two. In no case are they found free in the tissue, outside the vessels. Their frequency in the capillaries of some kidneys, their scarcity or absence in others, and the absence of inflammation of the tissues about them, suggest that their presence in large numbers represents postmortem growth within the vessels.

THE KIDNEYS IN LOBAR PNEUMONIA

Among the cases studied there are 32 examples of lobar pneumonia. There is cloudy swelling in the kidneys of all of them. Six, or 18

per cent, are the site of more advanced injury of very moderate extent. In five of these six haemorrhages have been found within a few scattered groups of tubules.

The most conspicuous changes, however, are found in the tubular epithelium. The cells are vacuolated, with a loss of substance into the lumina of the tubules, and consequent flattening of the epithelium already described. Fresh necrosis of a few cells scattered here and there is present in all six of the kidneys, and in four there is calcification of the necrotic epithelium. In one of the kidneys the cells of a number of tubules show the familiar colloid transformation.

In summary, among 32 cases of lobar pneumonia there was no instance of severe diffuse acute nephritis. In the kidneys of six there were rather marked changes in the epithelium, and in five a few haemorrhages from the glomeruli were found. No thrombi were seen in any of the glomerular capillaries.

SUMMARY

Acute nephritis has been found in 9.4 per cent of ninety-five examples of pneumococcal infections of various kinds (lobar pneumonia, organizing pneumonia, empyema, pericarditis, otitis media and meningitis).

The microscopical character of the nephritis corresponds to that produced in rabbits by the intravenous injection of a toxin made from pneumococci.

The kidneys of young children seem especially susceptible to injury by the pneumococcal toxin. Outspoken examples of acute nephritis were found only in infants with pneumococcal infections, usually of long duration, other than pneumonia alone. It was not present in the kidneys of the adults studied who had similar chronic pneumococcal infections.

Slight or moderate changes, besides cloudy swelling, have been found in 76.8 per cent of the kidneys examined. This damage of slight degree, occurring in the kidneys of adults and children, differs only in extent from that found diffusely in the kidneys of infants with distinct acute nephritis.

LITERATURE

(1) LONGSCOPE, W. T.: *Jour. Clin. Invest.*, 1927, **5**, 7.
(2) LUKENS, FRANCIS D. W., AND W. T. LONGCOPE: *Jour. Exp. Med.*, 1931, **53**, 511.
(3) RICH, A. R., BUMSTEAD, J. H., AND M. FROBISHER: *Proc. Soc. Exp. Biol. and Med.*, 1929, **26**, 397.
(4) MACCALLUM, W. G.: A Text-Book of Pathology. 4th edition, 1928, 262.
(5) ERNST, PAUL: Inaug. Dissertation, Zur Aetiologie der Nephritis. Zurich, 1884.
(6) COUNCILMAN, W. T.: *Amer. Jour. Med. Sc.*, 1897, **114**, 23.
(7) HOLT AND HOWLAND: Diseases of Infancy and Childhood. 8th edition, 1925, 607.
(8) MACCALLUM, W. G.: A TEXT-BOOK of Pathology. 4th edition, 1928, 267.
(9) FAHR, TH.: Henke-Lubarsch, Handb. d. spez. path. Anat. u. Hist. Fünfter Band, Zweiter Teil, 1929, 285.
(10) ASCHOFF, LUDWIG: Pathologische Anatomie, Vierte Auflage, Spez. Teil, 1919, 521.
(11) BLACKMAN, S. S., BROWN, J. H., AND G. W. RAKE: *Bull. Johns Hopkins Hosp.*, 1931, **48**, 74.
(12) MCGREGOR, L.: *Amer. Jour. Path.*, 1929, **5**, 545.
(13) RICH, A. R.: *Bull. Johns Hopkins Hosp.*, 1929, **44**, 283.
(14) JACKSON, HENRY, JR.: *Amer. Jour. Path.*, 1927, **3**, 285.

A STUDENTS' BIBLIOGRAPHY OF INTERNAL MEDICINE: TYPHOID FEVER

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In dealing with successive classes of students the writer has been puzzled to understand why it is so difficult to arouse in them any serious interest in the historical side of medicine. Surely one would expect a study as fascinating and as essential to the adequate understanding of disease to be eagerly pursued. Gradually the conviction has grown that it is not the substance of the subject but the conventional method of treatment, both in textbook and in colloquium, which is at fault, and that if one commences the discussion not with the nebulous beginnings of medicine but at an epoch psychologically and scientifically not too remote from present-day knowledge and thought, the student will follow the argument with interest. Otherwise he will become lost, nine times out of ten, in the morasses of ancient and medieval mysticism and will abandon entirely this method of approach. Let it not be thought that we question for a moment the importance of medical historical studies as an academic discipline or as a vital part of the story of the development of civilization, but after all it is too much to expect of the average medical student who is not primarily an historical philosopher that he have much patience with primitive ideas of miasmas, humors and effluvia or that he take very seriously therapeutic suggestions which might well have emanated from a witch's cauldron. Knowing that the blood circulates as it does, the fancy of its darting back and forth in the vessels soon becomes tiresome to one who is trying to follow the development of ideas which have led up to modern concepts of the circulation, just as the doctrine that fevers are manifestations of disordered humors can bear no possible relation to any present-day concept of infectious disease. Nor does the attitude of some teachers who try, as it were, by a process of artificial respiration, to endow the subject with life and to read into some fantastic treatise analogies to actual facts help the

matter in the least. The student is usually left not only unconvinced but with a feeling that the whole thing is not worth while.

If this be true, it remains to select some logical point from which to start historical discussions, if possible, that point at which scientific (and medical) thinking shook off the mysticism of tradition and physicians began to observe phenomena as they actually exist. The beginning of the nineteenth century may fairly be taken as such a landmark, at least as regards medicine. The emancipation of the French and English clinicians, the development of physical diagnosis, the application in the clinic of post-mortem control and soon thereafter of exact and graphic methods all indicate a mode of approach kindred to our own. That earlier brilliant discoveries stand out here and there is, of course, evident; these may profitably be studied in retrospect, in relation to a later more continuous story of development.

But the acquisition of historical information must, after all, be left largely to the student himself; he must read and he must be led from one phase of the subject to another by his own interests. A readily accessible bibliography becomes, then, a matter of prime importance. Where, with his limited time can he turn to find out what is really worth while on any given subject? Huge compendia of references are discouraging and most of the briefer ones are inadequate and make little attempt to confine themselves to fundamentals. It occurred to us that a bibliography of important topics in internal medicine, moderate in scope but definitive in the sense of including every fundamental contribution and of omitting nothing of prime importance, would be of value. Brief critical comments, furthermore, on individual items might enhance its suggestiveness.

When we embarked on this project some time ago, it was our purpose to deal with various phases of internal medicine in a volume of, perhaps, some five or six hundred pages. It soon became evident, however, that the task, if properly done, would be impossible for a single person unless he had at least his full time to devote to it; the collection of the bibliography of typhoid fever which is herewith submitted occupied all of the writer's spare hours over a period of some six months. But having become more and more convinced of the soundness of the idea, we wish to present this fragment as a demonstration of what can be done, in the hope that others may take up the task along similar lines.

In collecting what is now presented, the "pedigree" of each book or article has been scrutinized with the greatest care and there have been included only contributions which stand out because a new idea is developed or because a subject is summarized in more or less definitive form. To this end every title has been inspected and in many cases collated by the writer, a task made easy by the readily accessible stacks of the Lane Library. Roughly speaking, this is a nineteenth century bibliography although a few more recent references of compelling importance in a sense bring it up to date.

Real difficulty was at once encountered in deciding where to draw the line when following back the main stem of some disease to its roots in the biological sciences. And what to do about collateral branches? Should one include an elaborate bibliography on the bacteriology of typhoid, on the public health aspects, or on the results of typhoid inoculation when dealing with that disease? To what extent should one refer to fundamental contributions on metabolism in connection with diabetes or to purely haematological studies in connection with pernicious anemia? Obviously there is nowhere a sharp boundary nor should one try to establish one. The thought has been constantly in mind, however, that this is essentially the bibliography of a clinician. Hence, such references as deal with non-clinical matters have been only those which have a direct application to some fundamental aspect of the disease, which involve an important discovery or which summarize a certain biological aspect so that the student may have a starting-point for further reading.

Finally came the question of languages and for the most part we have confined ourselves to English, German and French titles. But within these limits no discrimination has been practised, and if here or there one language seems to predominate, it is no more than the expression of our search for the truth.

Typhoid fever

General Articles and Texts.....1, 2, 3, 4, 5, 7, 10, 12, 30, 31; 34, 37
Definition.....1, 2, 3, 4, 5, 7, 8, 9
Pathology.....1, 2, 3, 4, 5, 29, 44
Contagiousness.....6, 7, 11, 12
Immunity.....6, 7, 20, 23, 41

Differentiation from Typhus....8, 9
Mode of Transmission....11, 12, 32
Etiology....14
Bacteriology....14, 15, 16, 17, 18, 21, 40
Blood count....19
Paratyphoid....22
Epidemiology....13, 32, 33, 39
Carriers....32, 33, 39
Artificial Immunization....20, 23, 24, 28
Diagnosis....25, 26, 27
Treatment....35, 36, 38, 42

For a good review of the early literature on typhoid fever see Gay (ref. 43). It should be remembered that up to the nineteenth century clinical medicine was dominated largely by the Galenic point of view and that fevers were thought of in terms of vague influences, alterations of humors and so on. Even keen clinical observers such as Huxham were so influenced by fantastic ideas of pathological physiology that their clinical descriptions, while objective, are largely meaningless. For the most part it is impossible to determine with just what conditions the observer was dealing.

1. *Huxham, John:* An Essay on Fevers, to which is now added a Dissertation on the Malignant, Ulcerous Sore-Throat. London (S. A. Cumberlege), 1782.

The Essay is of importance partly because it represents the contemporary point of view on fevers in general, and partly because Huxham is credited with being one of the first to differentiate, under the names of "slow nervous fever" and "putrid malignant fever" typhus and typhoid fevers. The accounts are, however, largely unintelligible and contain nothing definitive except, perhaps, the following passage from the account of putrid fever (p. 96): "The Stools, especially near the State, or in the Decline of the Fever, are for the most Part intolerably stinking, green, livid, or black, frequently with severe Gripes and Blood. When they are more yellow, or brown, the less Danger; but the highest, when they run off insensibly, of whatever Colour. It is likewise a very bad Symptom when the Belly continues hard, swoln, and tense after profuse Stools; for this is generally the Consequence of an Inflammation, or Mortification of the Intestines."

2. *Chomel, A. F.:* Des Fièvres et Des Maladies Pestilentielles. Paris (Crochard), 1821.

During the early part of the 19th century there arose the remarkable school of French clinician-pathologists typified in the present instance by Chomel and Louis. Emancipated entirely from the domination of Galenic fantasy they described what they saw in the clinic and at postmortems with amazing clarity and exactness. As examples of simple but nice use of language these works remain unsurpassed in medical writing. Under the heading "La fièvre entéro-mesentérique" Chomel describes, briefly, what was undoubtedly typhoid fever, and went a step ahead of his contemporaries, who had already observed intestinal ulceration in association with fevers, by regarding the ulcers as a feature of the disease rather than its cause. His ideas on epidemiology and contagion were indefinite and he merely emphasizes the observed fact that "entéro-mesentérique" affected young people especially, and furthermore, those who were relatively new-comers in Paris and who found themselves under altered conditions as regarded "air, food, drink and occupation."

"The progress of the disease does not differ much from that of ordinary adynamic fever, unless it be in respect of the following symptoms: There is, in the second period, pain or tenderness on pressure in the right flank, diarrhoea, meteorism, and on opening the body one regularly finds ulcers of the intestines. It has been alleged that the intestinal ulcers precede the febrile movement, but the facts upon which this opinion is based do not seem to us sufficient to support it" (p. 187).

"If one opens the intestine throughout its extent with a scissors, and examines with care the alterations of which it is the seat, one encounters this remarkable fact: the internal surface presents ulcers, the more abundant, larger and deeper the nearer they are to the cecum and its valve . . . ." (p. 192). "In some cases the serous membrane is the only one which is not destroyed; in others, even it is perforated and the intestinal canal communicates with the cavity of the peritoneum; fecal material has in this way been able to escape, and give rise to an inflammation which has precipitated the end of the subject" (p. 193).

Despite this admirable description Chomel was not entirely clear

or complete in his definition of the disease, and it remained for Louis (see ref. 5) to give a definitive description. As regards distinction from typhus, Chomel states (p. 189) "We will expose the distinctive signs of these two affections later." However, the only subsequent passage bearing on this point deals with it indirectly and occurs in a discussion of the significance of intestinal ulcers in fevers: "One can not, then, reasonably conclude that the disturbance of general function which one observes in this disease be the effect of the lesion of the digestive tube. The intestinal ulcers are to putrid fever (typhoid and perhaps some other disorders) what buboes are to plague and to anthrax, *and what its proper eruption is to typhus*, namely, one of the phenomena of the disease and not the entire disease" (p. 234).

3. De la maladie à laquelle M. Bretonneau, médecin de l'hôpital à Tours, a donné le nom de dothinentérie, ou dothinentérite; par M. Trousseau, D.M.P. ancien interne du même hôpital. Archives Générales de Médicine, 1826, x, 67, 169.

The recognition of typhoid as a definite entity was in the air for some years before the definitive descriptions of Louis (see ref. 5) and others. The idea of considering fevers in general as manifestations of a morbid state caused by miasm, atmospheric or telluric conditions, was being questioned and various entities were being separated. While local and diffuse intestinal lesions were being found and described in certain fevers, their relation to the disease in question and to dysentery in general was not yet clear. Trousseau's paper is of importance in the history of typhoid for two reasons: first, because it includes an analysis (somewhat polemic in style) of the contradictory views on fevers which agitated the physicians of the time (Prost, Petit and Serres, Broussais, Andral, and others) and secondly, because it champions the priority of Trousseau's chief Bretonneau, who is claimed to have clearly defined the clinical, and anatomical features of typhoid under the name of dothinentérite as early as 1813. "He had been led to define a disease the seat of which seems to be exclusively in the glands of Peyer and of Brunner, which one encounters in the jejunum, ileum and large intestine. He has . . . . outlined the symptoms, has described precisely the manifestations of the malady on successive days and has summarized the diagnostic points so clearly that there

are few of his pupils who do not clearly distinguish this form of 'entérite' from all others" (p. 67). There follow excellent case reports with pathological notes especially on the intestinal ulcers.

4. Cases showing the Frequency of the Occurrence of Follicular Ulceration in the Mucous Membrane of the Intestines, during the Progress of Idiopathic Fevers; with Dissections, and Observations on its Pathology. By Cornwallis Hewett, M.D., Physician to St. George's Hospital. The London Medical and Physical Journal, 1826, lvi, 97.

Hewett's report should be included in the bibliography because it is the first English account of typhoid which approaches completeness. The clinical features are well described as are the pathological changes. However, the subject still remained confused and Hewett distinctly follows the French observers and does not take the lead. It is not clear from his account as to how far he was convinced that typhoid was actually a specific disease; rather one gets the impression that he regarded it as a reaction type of fevers in general. The descriptions of cases by Bright in the following year (Reports of Medical Cases, London, 1827, I, 178) certainly refer to typhoid but are also noncommittal as to the implications of the disease.

5. *Louis, P.—Ch.—A.* RECHERCHES anatomiques, pathologiques et thérapeutiques sur la maladie connue sous les noms de GASTRO-ENTÉRITE, fièvre putride, adynamique, ataxique, typhoïde, etc, etc., comparée avec les maladies aïgues les plus ordinaires. Paris (J. B. Baillière) 1829. 2 vols.

"In order to know how to proceed with a problem which could not be properly clarified by simple discussion, I collected, from 1822 to 1827, the histories of all the patients taken with acute diseases who were admitted to the Charité in the wards Saint-Jean and Saint-Joseph at that time in charge of M. Chomel. I assembled . . . . one hundred and thirty-eight observations of 'typhoid' fever of which fifty pertained to individuals who died. I have analyzed them all in order to find out which among the numerous lesions were proper to the 'typhoid affection,' and I have compared them to the alterations found as a consequence of other acute disorders in eighty-three sub-

jects whose histories I had also collected. I made the same study with reference to symptoms both in the patients with typhoid and with other acute affections whether they recovered or died; in brief, I analyzed the visceral alterations in one hundred and thirty-three subjects and the symptoms in nearly nine hundred.

"I have discarded from the material the facts which seemed to lack exactness, and when I drew my conclusions from the rest I had ever in mind this thought of the author of Emile: 'I know that truth lies in things and not in my mind which judges them, and the less of myself I put into the conclusions which I draw the more certain I am of approaching the truth' ". (Introduction, p. IX).

Upon these observations Louis based his description of typhoid (which he separated clearly from other fevers) and to which no important clinical or gross anatomical fact has since been added. While the way had been prepared by others, to Louis belongs the credit of the first complete detailed analysis of the disease. He recognized fully that the essential lesions were those of the intestine, mesenteric lymph nodes and spleen and separated from them secondary and incidental findings. The clinical picture is admirably drawn, including detailed discussions of rose spots, intestinal hemorrhage and perforation. With regard to etiology Louis maintains a conservative attitude and admits frankly that the cause of typhoid is unknown. His statistics, however, confirm the impressions current at the time that most of the cases occurred in young people recently come to Paris. No comments are made on the question of contagion. A point of special interest is the obvious severity of the typhoid fever of Louis in contrast to that of today. The onset was usually abrupt and stormy, often with chills and the early appearance of diarrhoea and stupor. In almost one fourth of Louis' fatal cases death occurred as early as the second week, of "toxaemia" or secondary infection, and the general mortality was nearly 30 per cent. Septic complications, partly the result of neglect and poor hygiene doubtless, were frequent, including erysipelas, suppurative angina and abscesses following the application of blisters.

Louis departed deliberately from the mystic traditions of ancient medicine: "It is not inappropriate to remark at this point that one can not depend upon the authority of the ancients in questions relative

to the seats of disease, since these questions can only be cleared up by comparison of symptoms with lesions and the ancients were ignorant of pathological anatomy. Neither is it true, as is often said, that facts do not grow old. Without doubt some well observed facts do not grow old and can not grow old, but the immense majority has grown old and those which we gather today will grow old in their turn, for they carry more or less the imprint of the time, of its methods, more exact than those of previous periods and less rigorous than those which will follow us. It behooves those who devote themselves to observation to be impressed by this truth and to realize that the best work is only good in relation to its time and that it awaits another, more exact and more complete." (Preface p. Vii, footnote 2).

6. Notice sur la contagion de la dothinentérie; lue à l'Académie royale de Médecine, le 7 juillet 1829, par M. Bretonneau, médecin de l' hôpital de Tours

Archives Générales de Médicine, 1829, xxi, 57.

While the question of the contagiousness of typhoid had been raised and supported by the observation of scattered outbreaks in rural districts, it was generally held by urban physicians that the disease was not transmissible. Bretonneau was one of the first to attract serious attention to the probability of contagion in a spirited address before the Academy. He opens "Typhoid fever is contagious; it is contagious in Paris, and nowhere is it more often contagious" (p. 57). "Often imported into a village, one sees it spread from the patient to some of the attendants. It then spreads from the affected family to another, and one generally observes that it is not to the nearest family. but to those whose contacts have been most intimate and frequent" (p. 59). He proceeds to assemble many unassailable instances of spread of the disease by contagion and answers the main arguments to the contrary. Bretonneau was also one of the first to insist on the immunity produced by an attack.

7. *Smith, Nathan:* A Practical Essay on Typhous Fever. New York: E. Bliss and E. White, 1824.

The Essay is of special importance first, because it is one of the earliest accessible accounts of typhoid fever in America and secondly,

because of Smith's clear recognition of the contagiousness of the disease. One regrets that the writer's hint of a subsequent enlargement of the work was never fulfilled. However, all the essential features are described. "The Typhous Fever, ... is a disease sui generis, exhibiting as little variety in the different individuals affected by it as some of the diseases which are acknowledged always to arise from contagion" (p. 15). "There is another marked point of analogy between Typhus[1] and the common contagious maladies, which is, that it rarely affects the same individual twice" (p. 16). ". . . . for during the twenty-five years since I first attended patients in this disease, and in that time I have visited many hundreds, and have witnessed its prevalence several times in the same village, I have never known or heard of its recurrence in the same person" (p. 17). "That the Typhous Fever is contagious, is a fact so evident to those who have seen much of the disease, and who have paid attention to the subject, that I should have spared myself the trouble of saying anything with regard to it, did I not know that there are some physicians in this country, who still dispute the point; one, which I think can be as fully demonstrated, as that the measles, small-pox, and other diseases universally allowed to be contagious, are so" (p. 11). This assertion is elaborated and supported by specific instances.

8. Observations suggested by a Comparison of the Post-Mortem Appearances produced by Typhous Fever in Dublin, Paris, and Geneva. By H. C. Lombard, Physician to the Geneva Hospital; (communicated in a letter to Dr. Graves). Dublin Medical Journal, 1836, x, 17. Second letter from Doctor Lombard to Doctor Graves on the Subject of Typhous Fever. Dublin Medical Journal, 1836, x, 101.

Lombard was thoroughly familiar with typhoid on the Continent and believed the intestinal lesion to be a constant one, although the English physicians did not at this time agree with the claims of the French in regard to a specific ulceration of Peyer's patches. On visiting Ireland, Lombard saw cases which seemed to be the same disease, but to his surprise no intestinal lesions were present at autopsy.

[1]Probably a misprint; Smith evidently meant Typhous (Typhoid).

The two letters are a summary of Lombard's reflections on his curious experience; he hit on the correct solution and concludes the second letter as follows: "You have two different fevers, one highly contagious, which I may call the *Irish Typhus*, and in which the cephalic symptoms predominate, to the exclusion of abdominal alterations; the other which is *sporadic*, and most likely not so infectious, and in which the abdominal symptoms are more predominant. . . . ."

These letters had a great influence in stimulating accurate differentiation of typhoid from other fevers.

9. Gerhard on Typhus Fever. Art 1. On the Typhus Fever which occurred at Philadelphia in the Spring and Summer of 1836; illustrated by Clinical Observations at the Philadelphia Hospital; showing the distinction between this form of disease and Dothinenteritis or the Typhoid Fever with alteration of the follicles of the small intestine. By W. W. Gerhard, M.D., one of the Physicians to the Hospital. American Journal of the Medical Sciences, 1836, xix, 289–322.

Part II. American Journal of the Medical Sciences, 1837, xx, 289–322.

Although typhoid was being recognized by many as a distinct entity, there was still considerable confusion with other fevers especially typhus. To Gerhard belongs the credit of definitive differentiation of typhoid from typhus on the basis of the cases which he studied in the wards of the Pennsylvania Hospital. Gerhard had been in Paris with Louis and like other Americans who had studied abroad recognized the identity of the disease in the two continents. He points out, however, that the British, while familiar with the intestinal lesions, regarded them as "a mere complication of ordinary typhus." An epidemic of typhus in Philadelphia gave him the chance to compare the two fevers. The anatomical lesions "were as different . . . . as the pustules of small-pox are unlike the eruption of measles" and in both were different from those found in remittent fever (malaria). In regard to the clinical features,—"When the disease is completely formed, the characters on which the distinctions between the two forms of fever rest are: 1. The suffusion of the eyes which occurs in every case, or nearly every case of typhus fever, with the dusky red aspect

of the countenance. 2. The extreme stupor and inactivity of the mind even when positive delirium does not exist. 3. We also observe in typhus no constant abdominal symptoms. . . . . 4. If to these symptoms be added the peculiar eruption of petechiae, which is scarcely ever absent in whites, there remains hardly a possibility of error. In typhoid fever we consider as distinctive characters, the prostration, the somnolence, the slow development of nervous symptoms, which are not so strongly marked as in typhus. The abdominal symptoms are tympanites, pains in the abdomen, and diarrhoea. The sibilant rhonchus is heard in the chest; and lastly, there is an eruption of rose-coloured papulae and sudamina upon the skin." He was sure typhus was contagious, but was not certain about typhoid.

10. *Bartlett, Elisha:* The History, Diagnosis and Treatment of Typhoid and of Typhus Fever, etc. Philadelphia: Lea and Blanchard 1842.

While Smith (see ref. 7), Jackson and others, had written briefly or incompletely on typhoid, Bartlett's book contains the first complete account of the disease in English. The article of 180 pages is a masterpiece of clinical writing and includes a careful analysis of current ideas with temperate and well-reasoned conclusions. Bartlett accepted the idea of the contagiousness of typhoid, recognized that the etiology was unknown but felt that the disease was specific and concludes his work with this remark "which disease, thus characterized and defined, differs essentially from all others, in its causes, in its symptoms, in its lesions; and is, in the present state of our knowledge, only to a limited extent under the influence of control of art" (p. 180).

11. *Budd, William:* On the Fever at the Clergy Orphan Asylum. Lancet 1856, II, 617.

Budd, William: On Intestinal Fever: Its Mode of Propagation. Lancet, 1856, II, 694.

While various writers such as Gendron and Bretonneau, in France, and Nathan Smith, in America, had already insisted on the contagiousness of typhoid it remained for Budd to give such an impetus to the idea that it was soon accepted by many physicians. His papers are convincing examples of keen observation and clear logic. Budd

stressed the importance of the bowel discharges in the transmission of the disease and sensed the existence of carriers (*v. infra*). "This species of fever has two characteristics: the first is that it is an essentially contagious disorder; the second that by far the most virulent part of the specific poison by which the contagion takes effect is contained in the diarrhoeal discharges which issue from the diseased and exanthematous bowel. The first case in the series may either be casual and imported, or may be due to the local rekindling, through atmospheric or other changes, of poison which had remained as the dormant legacy of some previous attack." He went wrong in thinking the poison might diffuse from the excreta through the air, but he suggested the following prophylaxis: "These measures are founded on the power of chemical agents to destroy the infectious properties of contagious poisons. If it be certain that the intestinal discharges in this fever are the principal means of propagating the disease, it is no less certain that by subjecting the discharges on their issue from the body to the action of powerful disinfectants, they may be entirely deprived of this property." He used chloride of zinc.

Budd lamented the attitude of the Metropolitan Board of Health and of the Royal College of Physicians who, like the Paris Academicians in Bretonneau's day, opposed the idea of contagion and believed that the disease was generated by filth. In describing the epidemic at North Tawton, a town in which there had been no typhoid for years, he points out that the lack of sanitation could not alone be held responsible for the outbreak. He describes the dirty privies near the houses, the dung-heaps and the pigs. "Nevertheless, these things existed for many years without leading to any of the results which it is the fashion to ascribe to them. Much there was, as I can myself testify, that was offensive to the nose, but fever there was none. In the course of time—as, was indeed, sure to happen—this element was at length added, and it was then found that the conditions which had been without power to *generate* fever, had but too great power in promoting its spread, when once the germ of fever had been introduced."

Budd sustained his thesis in subsequent articles and finally gathered all his data into a book (see ref. 13).

12. *Murchison, Charles:* A Treatise on the Continued Fevers of Great Britain. London: Parker, Son and Bourn, 1862.

To Murchison belongs the credit of the first encyclopedic treatise on typhoid fever. The section on this disease which comprises some two hundred pages has influenced practically every succeeding account up to the present time. Points of especial importance are the elaborate catalogue of the nomenclature of the disease, a masterly, well documented historical sketch with special attention to the distribution of typhoid and typhus fevers in England, the elaborate statistics as to geographical distribution, age, sex, season, etc., the mortality statistics and the vivid and accurate clinical descriptions. There are several exquisite colored plates depicting the distribution of rose-spots. The discussion on contagion is of especial interest, since Murchison held out against the idea that typhoid was communicable and insisted on its origin from the emanations of sewage. In fact he described the disease under the name of "pythogenic" fever—(arising from putrescence). Most of Murchison's arguments against contagion can be explained by the doctrine of "carriers."

13. *Budd, William:* Typhoid Fever: Its Nature, Mode of Spreading and Prevention. London: Longmans, Green and Co., 1873.

In this book, already referred to above (see ref. 11), the writer collects in a definitive matter his observations on the spread of typhoid fever. He levels his batteries, masked by the most delicate satire, at the anticontagionists, and attacks especially the pythogenic theory which carried the authority of Murchison's support. His final devastating argument against the spontaneous generation of typhoid from putrescent matter was based on the epidemiological facts of "the hot months of 1858 and 1859, when the Thames stank so badly." "The occasion, indeed, as already hinted, was no common one. An extreme case, a gigantic scale in the phenomena, and perfect accuracy in the registration of the results—three of the best of all guarantees against fallacy—were all combined to make the induction sure. For the first time in the history of man, the sewage of nearly three millions of people had been brought to seethe and ferment under a burning sun in one vast open cloaca lying in their midst. The result we

all know. Stench so foul, we may well believe, had never before ascended to pollute this lower air. Never before, at least, had a stink risen to the height of an historic event. Even ancient fable failed to furnish figures adequate to convey a conception of its thrice Augean foulness. . . . . At home and abroad, the state of the chief river was felt to be a national reproach. 'India is in revolt, and the Thames stinks' were the two great facts coupled together by a distinguished foreign writer, to mark the climax of a national humiliation. . . . . Meanwhile the hot weather passed away; the returns of sickness and mortality were made up, and, strange to relate, the result showed, not only a death rate below the average, but, *as the leading peculiarity of the season*, a remarkable diminution in the prevalence of fever, diarrhoea, and the other forms of disease commonly ascribed to putrid emanations. . . . . So that while pythogenic compounds were poisoning the air with what may be called a forty-thousand fever power the so-called pythogenic fever, so far from rising in proportion, fell much below its average" (p. 148).

The more important parts of the book, however, are those which deal systematically with the modes of transmission. Budd showed by well-documented studies of numerous outbreaks that the bowel discharges were the main source of infection, that the disease was water-borne and that milk, food, contaminated linen and fomites in general were sources of dissemination. He erred in insisting that the contagion might be air-borne and that the emanations from a sewer or water-closet contaminated with the discharges from typhoid patients were dangerous. He insisted, however, on a specific virus as the *sine qua non* of typhoid and recognized the minute size of the "germ" and its capacity for multiplication.

The work is a masterpiece of exposition, argument and fine rhetoric.

14. *Eberth, C. J.:* Die Organismen in den Organen bei Typhus abdominalis. Virchow's Archiv, 1880, lxxxi, 58. (Juli).

The discovery of the typhoid bacillus is generally ascribed to Eberth. His were, however, by no means the first attempts to find a microbic cause, and the present paper was preceded by numerous reports describing the presence of various bacteria in the tissues of patients dead

of typhoid. These were, for the most part, obviously saprophytes or secondary invaders. The technical difficulties of studies of this sort sixty years ago must be kept in mind; the modern methods of fixing, cutting and staining had not yet been devised. Eberth treated alcohol-hardened tissues with acetic acid and in some cases stained with methyl violet and Bismarck brown. Masses of bacteria were found in a good many cases, especially in spleen and mesenteric lymph nodes. They are described as tiny rods, at times with one or more spore-like bodies. The description seems far from conclusive; however, it is likely that Eberth was dealing with typhoid bacilli, at least in a good many instances. The article concludes: "These findings make it highly likely that the organisms found in the organs in typhoid fever stand in a [causal] relationship to the process."

Priority has been claimed for the observations of Klebs which appeared in April 1880 (Der Ileotyphus eine Schistomycose, Arch. f. Exp. Path. u. Pharm., 1880, xii, 231), but while Klebs may well have seen typhoid bacilli, the description is not very satisfying, especially the reference to thread-like forms 80 mikra in length.

Koch (Zur Untersuchung von pathogenen Organismen, Mitth. a.d. Kais. Ges., 1881, I, 45) reports the finding in tissues of typhoid patients of bacteria which seem to correspond to those described by Eberth; he suggested that Klebs' organisms were secondary invaders as he found them only on the surface of necrotic ulcers.

15. *Gaffky:* Zur Aetiologie des Abdominal typhus. Mitth. a.d. Kais. Ges., 1884, II, 372.

Gaffky's paper is a landmark in the bacteriological study of typhoid. By better methods of staining bacteria in tissues he confirmed the observations of Eberth and of Koch and showed beyond question that bacillary forms were almost always present in the tissues of typhoid-fever patients, especially in the spleen, liver, intestinal lymphoid tissue and, to a lesser extent, in the kidney. He pointed out clearly that the great variety of bacteria found in the superficial parts of the ulcers were probably secondary and unessential and that such organisms were not found in the depths of the diseased tissues.

But most important, he cultivated the bacilli from the spleen on slides coated with gelatin, isolated them in pure culture and described

accurately various characteristics including motility. He was unable to grow the organisms from stools or blood and failed to produce anything resembling typhoid fever in animals by inoculation of pure cultures in various ways although others had claimed that they had produced the disease with material from typhoid cases.

The review of the literature is definitive to date and analyzes the whole problem of the bacteriology of typhoid fever in a sound and temperate manner at a time when bitter struggles for priority were likely to color medical writing.

Gaffky was disappointed at being unable to produce the disease in animals but wisely concluded that this did not exclude the bacillus as the cause of typhoid and that further observations would be necessary to settle the question.

During the next few years after Gaffky's report, typhoid bacilli were cultivated from blood, urine, stools and other material *intra vitam*. For detailed references see Gay (ref. 43).

16. *Pfeiffer, A.:* Ueber den Nachweis der Typhusbacillen im Darminhalt und Stuhlgang. Deut. Med. Wchnschr., 1885, xi, 500.

Credit for first isolating typhoid bacilli from the stools is usually given to Pfeiffer. The paper is of great interest because of the technical difficulties. Colonies were fished from plain agar plates and identified by appearance of the growth on potato. No fermentation or agglutination tests were available at that time, nor had differential plates been developed. It is questionable, however, whether Pfeiffer's criteria were altogether adequate and whether his diagnosis of typhoid bacilli was invariably correct.

Pfeiffer is apparently the first to have cultivated the bacillus from material outside the human body.

17. *Hueppe:* Fortschr. d. Med., 1886, iv, 447.

In reviewing an article by von Fodor on bacteremia Hueppe states that he was able to cultivate typhoid bacilli from the urine in one of 18 cases. This is apparently the first record of a successful attempt.

18. *Neuhauss, R.:* Nachweis der Typhus bacillen am Lebenden. Berl. Klin. Wchnschr., 1886, xxiii, 89.

Many attempts to demonstrate typhoid bacilli in the blood during life were reported at about this time. Some of them consisted of direct microscopic study of the blood, others involved cultures of drops of blood obtained by incising rose spots or other areas of skin. Neuhauss, by the latter procedure, apparently was the first to obtain a positive culture. It was not until years later when larger amounts of blood drawn from the vein were used that the procedure became of practical diagnostic value (Schottmüller).

19. *Tumas, L. J.:* Ueber die Schwankungen der Blutkörperzahl und des Hämoglobingehalts des Blutes im Verlaufe Einiger Infectionskrankheiten. Deut. Arch. f. Klin. Med., 1887, xli, 323.

Tumas was the first to report fairly complete studies of the blood-count in typhoid fever. He observed that leucopenia was almost invariably present. Thayer (Johns Hopkins Hospital Reports, 1894, iv, 83) made the first careful American studies and emphasized the diagnostic value of the blood-count.

20. *Beumer and Peiper:* Bacteriologische Studien über die ätiologische Bedeutung der Typhus bacillen. Ztschr. f. Hyg., 1887, II, 110.

In the course of attempts to produce typhoid fever experimentally it was found that mice which had survived an initial small dose of typhoid bacilli later survived a much larger injection. The writers clearly recognized the possible application of such immunization to man although they did not pursue the subject further at the time.

21. *Anton B., u. G. Fütterer:* Untersuchungen über Typhus abdominalis. Münch. Med. Wchnschr., 1889, XXXV, 315.

Fütterer first cultivated typhoid bacilli from the content of the gall-bladder at autopsy in typhoid cases. The identification was probably correct. He points out that the bile does not seem to have an inhibiting action on these bacteria. This work was the precursor of a host of studies which proved that the gall-bladder was readily infected by way of the blood stream and that it was a common situation for persistence of bacilli during the "carrier state." For further references see Gay (ref. 43).

22. *Achard, Ch., et R. Bensaude:* Infections paratyphoïdiques. Bull. et mém. Soc. méd. d. hôp., 1896, XIII, 820.

The fact that there were a variety of organisms which resembled the typhoid bacillus was already known. Achard and Bensaude were the first, however, to report cases resembling typhoid from which "paratyphoid" bacilli were isolated. They used the term paratyphoid in the sense of "resembling typhoid" rather than in the strict modern technical sense. The bacteriological distinction was made mainly on the basis of agglutination tests with specific sera.

23. *Pfeiffer, R., u. W. Kolle:* Ueber die specifische Immunitätsreaction der Typhusbacillen. Ztschr. f. Hyg., 1895–96, XXI, 203.

The development of immunization was a logical sequel to preliminary studies. Of these some of the most important were those of Pfeiffer and Kolle. In a series of clean-cut experiments they showed that the serum of typhoid convalescents contained substances which protected guinea-pigs specifically against lethal doses of typhoid bacilli and that similar protective substances could be developed in the serum of goats, following repeated injections of culture. These observations together with practical results already obtained in cholera suggested attempts at human prophylaxis.

24. *Pfeiffer, R., u. W. Kolle:* Experimentelle Untersuchungen zur Frage der Schutzimpfung des Menschen gegen Typhus abdominalis. Deut. Med. Wchnschr., 1896, XXII, 735.

Pfeiffer's attempts at prophylactic vaccination were stimulated by encouraging results which had been obtained in cholera. Pfeiffer injected subcutaneously about 2 mg. of fresh culture scraped from agar slants suspended in broth and sterilized at 56°C. There was usually a chill within two or three hours followed by a rise in temperature to about 38.5°C. Only one injection was given. Serum drawn from the subjects about eleven days after the treatment was found to have as high a titer of protective bodies against experimental guinea-pig infection as the serum of typhoid convalescents. On this basis Pfeiffer hoped that the prophylaxis would convey as complete a protection as a spontaneous attack of typhoid fever, since at that time the

humoral bactericidal antibodies were regarded as entirely or almost entirely responsible for recovery from the disease.

25. *Gruber, Max, u. Herbert E. Durham:* Eine neue Methode zur raschen Erkennung des Cholera vibrio und des Typhus bacillus. Münch. Med. Wchnschr., 1896, XIII, 285.

It was found that serum from guinea-pigs immunized against cholera or typhoid developed the remarkable property when mixed with the bacteria in question under proper conditions of causing them to "stick together in large balls, and to lose their motility. We therefore have named these specific substances . . . . agglutinins." In discussing the implications of this finding Gruber and Durham laid special stress on the identification of unknown strains of bacteria by known immune sera. The alternative procedure of detecting specific immune bodies by testing against known cultures was, however, obvious and was later described from Gruber's laboratory by Grünbaum (see ref. 27).

26. *Widal F.:* Sérodiagnostic de la fièvre typhoïde. Sem. Méd., 1896, XVI, 259.

While Widal's name has been attached to the agglutination test in typhoid the original communication seems brief and inadequate and gives no credit to Gruber and Durham, who had already clearly described the phenomenon of agglutination. Widal added the patient's serum to broth cultures of typhoid bacilli in a proportion of 1 to 10 or 15 and incubated for 24 hours. Gross flocculation was observed at the end of this time.

27. *Grünbaum, Albert S.:* Preliminary Note on the Use of the Agglutinative Action of Human Serum for the Diagnosis of Enteric Fever. Lancet, 1896, II, 806.

Although Widal's paper appeared first, Grünbaum undoubtedly shares the credit for the development of this test, as his work was carried on in Gruber's laboratory during the preceding year and was the direct outcome of Gruber and Durham's work on agglutination. Grünbaum describes the microscopic method essentially as it is used today. "It is only in cases of enteric fever that the serum shows a

distinct agglutinative action within thirty minutes when diluted sixteen times, and hence this reaction can be used as a diagnostic sign."

28. *Wright, A. E., and D. Semple:* Remarks on Vaccination Against Typhoid Fever. Brit. Med. Jour., 1897, I, 256.

Wright and Semple's paper appeared shortly after that of Pfeiffer and Kolle. They imply, however, that Pfeiffer plagiarized the idea from a paper of Wright's which appeared on Sept. 16, 1896, in the Lancet, in which he claims to have put on record his first attempts at anti-typhoid inoculation. An inspection of this paper makes the implication seem unfair to Pfeiffer since, as the title would suggest (On the Association of Serous Hemorrhages with Conditions of Defective Blood Coagulability), the observations concern themselves with other matters.

While it is mentioned incidentally that a horse and two men received injections of typhoid bacilli in connection with the experiments on blood coagulability, there is not the slightest suggestion that the writer contemplated purposeful anti-typhoid prophylaxis. Pfeiffer's previous experimental work, furthermore, makes it evident that he already had the possibility of human immunization in mind.

Wright and Semple used essentially the same procedure as Pfeiffer, but measured the result in terms of agglutinative titer of the serum of the subjects. They found that such serum, even if rich in agglutinins, did not have any material bactericidal effect *in vitro*, and hence were more conservative than Pfeiffer in their conclusions as to the probable degree of protection which was to be expected.

Wright later described his results and those of others (Lancet 1902, II, 651).

29. *Mallory, F. B.:* A Histological Study of Typhoid Fever. Jour. Exper. Med., 1898, III, 611.

Important studies of the finer histological changes.

30. *Keen, William W.:* The Surgical Complications and Sequels of Typhoid Fever. Philadelphia (W. B. Saunders), 1898.

A definitive monograph based on a careful analysis of reported cases and enriched by the author's wide experience. It remains a

store-house of information on the (from the clinical standpoint) all important problem of typhoid complications.

31. *Curschmann, H.:* Der Unterleibstyphus (Wien, 1898, Alfred Hölder) in Nothnagel, H.—Specielle Pathologie und Therapie. Band III, I Teil, Wien, 1902.

The most comprehensive modern clinical treatise with important literature to date arranged with the subject matter.

32. *Koch, Robert:* Die Bekämpfung der Typhus. (Vortrag, gehalten in der Sitzung des Wissenschaftlichen Senats bei der Kaiser Wilhelms Akademie am 28 November, 1902). Veröffentlichungen aus dem Gebiete des Militär—Sanitätswesens. Berlin, 1903, Heft, XXI.

The control of typhoid epidemics was the outstanding problem of the disease at the end of the 19th century. While it was recognized that water and milk supplies contaminated by typhoid excreta were major factors, it had not been clearly appreciated that the most adequate way to check the spread of the disease was by disinfection of excreta at their source and isolation of the convalescent until they became bacillus-free. In this famous lecture Koch clearly outlined the logical methods of typhoid control. "There are therefore two conditions which must be fulfilled. In the first place we must be in a position to recognize the infectious agent with ease and certainty, and in the second place to dispose of it." To this end special methods of readily identifying the typhoid bacillus in the stools were developed (Drigalski and Conradi, Ztschr. f. Hyg., 1902, XXXIX 283) and stations were set up in typhoid districts for the control of carriers. These measures, together with improvement in sewage conditions, soon led to a great decrease in typhoid incidence in Germany.

33. *V. Drigalski:* Ueber Ergebnisse bei der Bekämpfung des Typhus nach Robert Koch. Centralbl. f. Bakt., 1 Abt. Orig., 1904, XXXIII, 776.

Drigalski's work amplified and extended that of Koch (see ref. 32) especially with reference to carriers who had never had clinical typhoid fever. Drigalski stressed the carrier as the main cause of continuous

endemic typhoid in distinction to extensive outbreaks due to contaminated water. He insisted on negative stool and urine cultures from convalescents before they were released from supervision.

34. *McCrae, T.:* Typhoid Fever, *in* Modern Medicine, Osler and McCrae, II, 70–231. (Lea Bros., Phila. and New York, 1907).

The best modern English article, based largely on the Johns Hopkins cases.

(Also 3rd ed., Lea & Febiger, Phila. and New York, 1925, I, 63–183.)

35. *Coleman, Warren:* Diet in Typhoid Fever. Jour. Amer. Med. Ass., 1909, LIII, 1145.

One of the most important contributions to the treatment of typhoid fever was the proof that a liberal diet could be taken with beneficial results. While various clinicians from Robert Graves (1835) on had empirically advised the feeding of typhoid patients, it remained for Coleman and his associates (see refs. 36, 38, 42) to establish by accurate scientific methods that food could actually be digested and absorbed and that nitrogen equilibrium could be maintained and weight loss prevented by high caloric diets. This was a radical departure from previous practice. Until the high calorie diet was introduced stress was placed on intensive hydrotherapy (see Brand, Die Hydrotherapie des Typhus, Stettin, 1861). With liberal feeding, however, it has been found that hydrotherapy can largely be done away with. One of the most notable results of the treatment is shortening of the period of convalescence, formerly so long and tedious.

The series of studies is of great importance not only in relation to typhoid but because the principles which were established apply to other prolonged fevers as well.

36. *Shaffer, Philip A., and Coleman, Warren:* Protein Metabolism in Typhoid Fever. Arch. Int. Med., 1909, IV, 538.

In carefully controlled metabolism studies of typhoid patients it is shown that destruction of body protein (and loss of weight) which had been ascribed not only to fever but to obscure "toxic effects" could be prevented by feeding 10 to 15 grams of nitrogen (60 to 90

gms. of protein) daily together with an adequate carbohydrate ration. Coleman and DuBois showed later, however (Arch. Int. Med., 1915, XV, 887), that there was a "toxic" destruction of protein in typhoid since patients might have a distinctly negative nitrogen balance on a diet which contained more than enough calories to cover heat production.

37. *Schottmüller, H.:* Die Typhosen Erkrankheiten, *in* Mohr und Staehelin, Handbuch der Inneren Medizin. I, 371–519. Berlin, Julius Springer, 1911.
Excellent summary with literature.

38. *DuBois, Eugene F.:* The Absorption of Food in Typhoid Fever. Arch. Int. Med., 1912, X, 177.
One of the principal arguments against liberal feeding in typhoid was disposed of by these experiments which showed that protein and carbohydrate could be absorbed as well as during health and that the absorption of fat was only moderately diminished.

39. *Ledingham, J. C. G., and J. A. Arkwright:* The Carrier Problem in Infectious Diseases. New York, Longmans, Green and Co., 1912.
An authoritative summary of the carrier problem.

40. *Kutscher, K. H.:* Abdominal typhus, *in* Kolle und Wassermann: Handbuch der pathog. Micro-organismen, II Aufl., Jena, Gustav Fischer, 1913, III, 717–836.
Comprehensive review of the bacteriology of typhoid.

41. *Fornet, W.:* Immunität bei Typhus, *in* Kolle und Wassermann: Handbuch der pathog. Micro-organismen. II Aufl., Jena, Gustav Fischer, 1913, III, 837–898.
Comprehensive review of immunological aspects of typhoid fever.

42. *Coleman, Warren:* The Influence of the High Calorie Diet on the Course of Typhoid Fever. Jour. Amer. Med. Ass., 1917, **69,** 329.
A summary of the end results of the treatment.

43. *Gay, F. P.:* Typhoid Fever. New York, The MacMillan Co., 1918.

A comprehensive summary of knowledge of the disease from the biological and epidemiological standpoint. The bibliography is especially well selected and complete.

44. *Christeller, E.:* Der Typhus abdominalis, *in* Henke-Lubarsch, Handbuch der Speciellen Pathologischen Anatomie u. Histol., IV Band, II Theil, p. 500–609.

Special emphasis on pathological changes. Extensive bibliography. Good colored plates of lesions, gross and histological.

BOOK REVIEWS

Aphasia in children. By ALEXANDER W. EWING. With an introduction by E. D. Adrian. 152 pp. 8°. $3.50. (*Oxford Univ. Press, 1930.*)

The book presents a brief account of the methods by which it was discovered that of ten congenitally 'aphasic' boys and girls, six suffered from a condition of partial deafness hitherto unknown and unstudied. Prior to this research they had been variously classed as aphasic, as totally deaf, or as having normal hearing and being totally or almost totally dumb from causes unknown. The symptoms which led to such varying conclusions are here traced to a condition of normal or relatively normal hearing for a certain range of low tones. This group of patients is therefore described as 'high frequency deaf.'

The author includes a critical summary of the development of speech and language, and reviews in a highly practical manner methods of testing the hearing capacity of normal and 'aphasic' children. There is a brief review of the literature on aphasia.

This book may serve as an introduction to the subject of aphasia in general and supplies a real need by contributing many hitherto unknown facts in the particular field of the aphasias in children.

The emphasis placed upon this special group of the 'high frequency deaf,' who can be helped greatly with special instruction, is a great step forward in the differential diagnosis and treatment of that great and as yet unexplored realm,—the aphasia.

J. H. C.

A Textbook of Psychiatry. By D. K. HENDERSON and R. D. GILLESPIE. Third Edition. Pp. 583. (*Oxford University Press, New York and London, 1932.*)

The appearance of the third edition of Henderson and Gillespie's textbook within two years of the second edition speaks clearly enough for its well deserved popularity. The first chapter shows but few changes (an account of Rüdin's work on heredity, of Lorenz and Loevenhart's work on stupor, and of the Mayor of New York's Committee on Drug Addiction). The chapter on epilepsy has been elaborated somewhat, the chapter on the Relations of Psychiatry and Law has been enlarged, and a new chapter on the Psychiatry of Childhood is the principal addition (pp. 488–536). This chapter fills a gap which unfortunately still exists in so many modern presentations of psychiatry. It is a strange fact that such highly representative books as those of Bleuler, Bumke, and Aschaffenburg's *Handbuch* pay practically no attention to the existence of the psychiatric problems occurring in childhood. Strecker and Ebaugh, in the third edition of their textbook, were to the reviewer's knowledge the first to offer a chapter on pathology of children in a practical and systematic form. It is pleasing to see that Henderson and Gillespie have taken up this very active phase of psychiatry as well.

In a general psychiatric textbook, the space devoted to children's personality problems must necessarily be restricted. One must, on the other hand, gratefully acknowledge that the authors have utilized the fifty pages which the chapter occupies in an instructive and helpful manner. Their pluralistic approach, devoid of any one-sided adherence to the one or the other exclusive school, is refreshing.

The enormous influence of the environment on the child's mental processes, the child's plasticity, the prominence of egoistic tendencies in the production of symptoms are given as the three cardinal points in the psychology of children, in distinction from adults, "as far as a distinction in this field can be drawn."

The sex factor is dealt with in an empirical, commonsense rather than a speculative manner. The value of recreation, the factors of parent-child relationships, and the nature of children's school difficulties are discussed briefly but satisfactorily.

In the classification we find a feature which does not seem to fit into the objective and concrete presentation, which keeps itself otherwise aloof from theorizing. We have reference to the group of disorders of the so-called "glycopenic" variety, into which migraine, crises of collapse, insomnia, night terrors, cyclical vomiting, etc., are squeezed. The assumption that these conditions can be made to cease by the administration of glucose alone, "although there is usually no hypoglycemia," has not been sufficiently proved; besides, we are justified in shrinking from any scheme which looks in children's psychiatric problems for one cause or mode of treatment alone.

The other groups in the classification are disorders of personality, behavior disorders, habit disorders, psychoneuroses, psychoses, epilepsy, mental deficiency, and mental disorders occurring with, and probably dependent on, some physical disease. The authors still work with the concept of "moral imbecility."

It is gratifying to see that the authors refrain from the usual hair-splitting differentiation between neurotic and neuropathic and psychopathic children. Hypochondriasis in children is not discussed, nor is there any mention of the practically universal period of resistance in the two to four or five-year-old children, which, in our experience, has occasionally led overanxious parents and physicians to become unnecessarily alarmed over supposed "personality changes" in essentially normal children.

Except for the immediate application of large doses of glucose in the "glycopenic" disorders, the therapeutic advice is based on the consideration of the various factors entering into the individual problem. It is, however, scattered over the chapter; it would be perhaps more helpful to have, however brief, an organized discussion of the principles and aims of psychiatric treatment of children's personality problems.

L. K.

Elementary Zoölogy for Medical Students. By L. A. BORRADAILE, Sc.D. Second edition, 397 pages. *(Oxford University Press. 1930.)*

The material of this book is largely drawn from its author's Manual of Zoölogy, and is especially addressed to British students preparing for First Medical Examinations. The introductory chapter contains very compressed accounts of life and

its energy, as manifested in metabolism and growth, irritability and automatism, reproduction and conjugation. What the author holds to be the first, and the only peculiar, characteristic of living beings is briefly stated thus: "In them there goes on a process that tends to preserve and to increase them and their kind. This process is known as *life*. The second characteristic of living beings is the presence in them of a substance known as *protoplasm*. This they share with things that have been alive and are now dead" (p. 1). The last sentence of this quotation can not well be reconciled with a further, and more careful, statement (p. 15): "The living part of the body of all animals is a soft, slimy substance known as *protoplasm*.

The next four chapters are devoted to the anatomy and physiology of the frog. The chapters on skeleton, muscles and viscera provide a good introduction to the study of vertebrate form and function, as exemplified in the frog. Chapter IV on the nervous system and sense organs is necessarily uneven and cursory. The sympathetic system is but briefly mentioned, and the cranial nerves are scarcely more than a list to be memorized. Some notice of the nerve components would have given this subject at least a general significance. In the last chapter on the frog, "Histology, the Germ Cells, Death", there is urgent need for expansion. Here two criticisms of factual matter must be made. The following is from page 89: "Every tissue belongs to one of four classes: it is either epithelial, skeletal, muscular or nervous." What of mesothelium and endothelium? There is a later statement to the effect that pavement epithelium lines the coelom, blood vessels and lymphatics. Certain fundamental distinctions are simply ignored. Again (p. 101), macrophages are said to be formed by several phagocytes flowing together to form a common mass of cytoplasm containing several nuclei. On what evidence is this important assertion made? Here, as throughout the book, the reader is entirely excluded from original sources. Subsequent chapters consider the following forms in no special reference to their taxonomic position: VI, amoeba; VII, paramecium and vorticella; VIII, malarial parasite; IX, hydra; X, earthworm; XI, crayfish; XII, cockroach; XIII, mosquito and house-fly; XIV, tapeworm; XV, dogfish; XVI, rabbit. The book closes with brief chapters on embryology, classification and evolution.

In the discussion of paramecium no mention is made of the process of nuclear reorganization known as endomixis. Also (p. 134) it is said that "the effect of unnatural conditions was in the long run too strong, the recurring periods of depression became more and more severe, and at last the whole brood died." This is the usual fate of kept paramecia, but that it is not the necessary fate was long ago proved by Woodruff. Also to an American reader it must seem odd to find no mention of genes, x or y chromosomes, oestrus, tissue culture, and in the enumeration of ductless glands no mention of corpus luteum, pancreatic islands, and no distinction as to the parts of the pituitary; also, odd to have the vitamines dismissed with the single word *mysterious*. The items just mentioned occupy such an important place among American contributions that we have come to regard them as of elementary international interest.

C. F. D.